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Dergimiz uluslararası EBSCO indeksinde yer almakta olup, dergimizin 2023 yılına ait üçüncü sayısını sizlerle paylaşmaktan mutluluk duyuyoruz. Yeni akademik dönemle beraber yayınlanan bu sayımızda toplamda 30 özgün makale yer almaktadır. Tüm çalışmaların ilginizi çekeceğine eminiz. Keyifli okumalar.

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Perinatal outcomes of pregnancies with prenatally diagnosed conotruncal heart defects: A tertiary center experience

Prenatal dönemde tanı alan konotrunkal kalp anomalisi tanılı gebeliklerin perinatal sonuçları: Tersiyer merkez deneyimi

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ÖZ

Amaç: Perinatoloji kliniğimizde prenatal dönemde tanı konulan ve takip ettiğimiz konotrunkal kalp anomalilerin alt tiplerini, bunların diğer yapısal ve/veya kromozomal anomaliler ile ilişkisini, konotrunkal defektin tipine göre perinatal sonuçları değerlendirmeyi ve sonucunda konotrunkal kalp anomalileri ile ilgili klinik deneyimlerimizi paylaşmayı hedefledik.

Gereçler ve Yöntem: Bu retrospektif çalışma Ankara Şehir Hastanesi Perinatoloji Kliniğinde 10.03.2020 ile 30.10.2022 tarihleri arasında prenatal dönemde konotrunkal kalp anomali tanısı almış 93 vakadan takip döneminde takipten çıkan postnatal sonuçlarına ulaşılamayan ve postnatal fetal ekokardiografi ile konotrunkal anomali tanısı doğrulanmayan 14 vaka çıkarılarak postnatal tanısı kesinleştirilmiş 79 hastayla gerçekleştirilmiştir. Primer sonucunumuz prenatal konotrunkal anomali tanılı gebeliklerin sonuçlarını ve anomalinin tipine göre eşlik edebilecek yapısal ve/veya kromozomal anomalilerle ilişkisini değerlendirmekti.

Bulgular: Çalışmamızda 79 vaka analiz edilmiştir. En sık izlenen konotrunkal kalp anomalisi Fallot tetralojisiydi (40.5%). Çalışmaya aldığımız 79 vakanın ortalama maternal yaşı 30.2 idi. Hastaların refere kliniğimize başvurduğu ortalama gebelik haftası 27.5 olarak hesaplandı. Gebelik sonuçlarını incelediğimizde 79 vakadan 9'nda (11.4%) gebelik terminasyon ile sonuçlanmıştır. Altmış dokuz (87.3 %) hastanın gebeliği canlı doğum ile sonuçlanmıştır. Hastaların 33 (41.7%) tanesinde konotrunkal anomaliye ek ekstra kardiyak yapısal anomali mevcuttu. En sık izlenen kromozomal anomali Trizomi 21 (6/15) di. Canlı doğan 69 vakanın ortalama doğum haftası 37, ortalama doğum kilosu 2797 gramdı. Yenidoğan döneminde mortalite oranı 37.6% (26/69) olarak hesaplandı. Ayrıca canlı doğan 69 vakadan 41'nde izole konotrunkal anomali tanısı mevcuttu.

Sonuç: Konotrunkal kalp anomalilerinin prenatal tanısı, eşlik edebilecek ek yapısal ekstrakardiyak ya da kromozomal anomalilerin spatanmasına katkıda bulunur, dolayısıyla ailerlere uygun danışmanlık ve uygun koşullarda doğum planlaması sağlar.

Anahtar Kelimeler: Konotrunkal kalp anomalileri, Fallot Tetralojisi, Fetal ekokardiografi

ABSTRACT

Aim: To evaluate the types of prenatally diagnosed conotruncal defects and their association with other structural or chromosomal abnormalities and to assess the perinatal outcomes according to the type of the conotruncal defect.

Materials and Method: We retrospectively reviewed the records of 93 pregnancies prenatally diagnosed with conotruncal heart defects in the Perinatology department of Ankara City Hospital between 10 March 2020-30 October 2022. 14 of 93 patients were not included to the study because of lost from follow-up or inaccessible postnatal outcomes. Main outcome was to assess the pregnancy outcomes of conotruncal heart defects according to the type of the defect and associated structural and/or chromosomal abnormalities.

Results: Seventy-nine pregnancies were evaluated in our study. The most common conotruncal heart defect was tetralogy of Fallot (40.5%). The mean maternal age was 30.2 year and the mean gestational week of admission was 27.5. The rate of pregnancy termination was 11.4% (9/79). Sixty-nine fetuses born alive hence, the rate of live birth was (87.3%). Associated structural extracardiac anomly rate was (41.7%). The most common chromosomal abnormality was Trisomy 21 (6/15). The mean birth week of live borns was 37 week and the mean birth weight was 2797 gr. Mortality rate in the neonatal period was 37.6% (26/69). In forty-one (59.4%) of live borns conotruncal heart defect was an isolated finding.

Conclusion: Prenatal diagnosis of conotruncal heart defects contributes to the detection of associated structural and chromosomal anomalies hence provides appropriate counseling to parents and planning of the birth in appropriate conditions.

Key Words: Conotruncal heart defects, Tetralogy of Fallot, Fetal Ecocardiography

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GİRİŞ

Konjenital kalp hastalıkları (KKH) en sık görülen yapısal doğumsal anomaliler olup canlı doğumlar içinde %0.4-1 oranında görülmektedir (1,2). Konjenital kalp hastalıklarının birçok farklı alt grubu tanımlanmıştır, kardiyak çıkış yollarını ve büyük arterleri etkileyen konotrunkal kalp anomalileri (KTA) bu alt gruplardan bir tanesidir. Embryolojik gelişim sırasında, aortikopulmoner yarıklanmada sorun sonucu gelişen konotrunkal kalp anomalileri prenatal dönemde tanı alan ve sendromik olmayan konjenital kalp defektlerinin %25-33 kadarını oluşturmaktadır (3).

Konotrunkal kalp anomalileri tanımı içinde; Fallot tetralojisi (FT), Çift çıkışlı sağ ventrikül (ÇÇSV), Trunkus Arteriyozus (TA) ve Büyük Arter Transpozisyonu (BAT) gibi anomaliler yer almaktadır. Konotrunkal kalp anomalilerinin etiolojisi net olarak bilinmemekle birlikte gelişiminde; kromozomal anöploidiler ve kardiyak gelişimde rol alan bazı tek gen bozuklukları suçlanmaktadır, bunların yanında çevresel ve epigenetik nedenler de suçlanarak hepsinin ortak sonucunda bu anomalilerin oluştuğu görüşü hakimdir (4,5). Konotrunkal anomalilere postnatal erken dönemde kateter bazlı veya cerrahi tedavi ile müdahale edilmediğinde mortalite oldukça yüksek seyredebilmektedir (6). Dolayısıyla daha önce birçok çalışmada da bildirildiği gibi bu anomalilerin prenatal dönemde tanı alması postnatal hipoksi ve periopreatif mortaliteyi azaltabilmesi açısından önemlidir (7,8). Ayrıca, bu anomalilere prenatal dönemde tanı konması, eşlik edebilecek kromozom anomalilerinin ve/veya ekstrakardiak diğer yapısal anomalilerin de daha ayrıntılı araştırılmasına ve saptanmasına yol açarak, ailelere multisipliner bir yaklaşımla danışmanlık verilmesine ve doğumun uygun tersiyer merkezlerde planlanmasına olanak sağlar. Tüm bu verilerin ışığında biz de bu çalışmamız ile, bir referans merkezi olan Perinatoloji kliniğimizde prenatal dönemde tanı konulan ve takip ettiğimiz konotrunkal kalp anomalilerin alt tiplerini, bunların diğer yapısal ve/veya kromozomal anomaliler ile ilişkisini, konotrunkal defektin tipine göre perinatal sonuçları değerlendirmeyi ve sonucunda konotrunkal kalp anomalileri ile ilgili klinik deneyimlerimizi paylaşmayı hedefledik.

GEREÇ-YÖNTEM

Bu retrospektif çalışma Ankara Şehir Hastanesi Perinatoloji Kliniğinde 10.03.2020 ile 30.10.2022 tarihleri arasında prenatal dönemde konotrunkal kalp anomali tanısı almış 93 vakadan takip döneminde takipten çıkan postnatal sonuçlarına ulaşılamayan ve postnatal fetal ekokardiografi ile konotrunkal anomali tanısı doğrulanmayan 14 vaka çıkarılarak postnatal tanısı kesinleştirilmiş 79 hastayla gerçekleştirilmiştir. Çalışma Etik onayı hastanemiz etik kurulundan alınmıştır (sayı no: E2-23-3487).

Çalışmamız için prenatal dönemde konotrunkal kalp anomalisi tanısı alan hastaların kayıtları ve verileri hastanemiz Perinatoloji kliniği merkezi kayıt sisteminden alınmıştır. Prenatal dönemde konotrunkal kalp anomali tanısı merkezimiz Perinatoloji yandal uzmanları tarafından yapılan fetal ekokardiyografi değerlendirmesi sonucu konulmuş ve/veya kesinleştirilmiş (KTA şüphesi ile refere edilen hastalarda) olup, postnatal tanı pediatrik kardioloğlar tarafından yapılan ekokardiografi ile doğrulanmış vakalar çalışmaya dahil edilmiştir. Perinatoloji merkezimizde tüm ultrasonografi değerlendirmeleri Voluson E-10 (GE HealthCare) ile yapılmıştır. Fetal ekokardiografik muayenede, kalp dört oda görünümü, ventrikül çıkışları, üç damar, üç damar trakea görünümü, kısa ve uzun akslar, büyük damarların lokalizasyonu birbirleriyle ilişkisi ve ventriküler arası septum sıralı segmental değerlendirme ile çoklu planlar kullanılarak ayrıntılı bir şekilde incelenerek not edilmiş ve prenatal tanı konulmuştur. Daha sonra tüm fetüslere kapsamlı bir şekilde kromozomal anoploidi belirteç taraması ve diğer tüm sistemleri kapsayan ayrıntılı anatomik inceleme yapılmıştır. Konotrunkal kalp anomalisi tanısı alan tüm hastalara perinatoloji uzmanı, tıbbi genetik uzmanı, yenidoğan uzmanı, çocuk kardiyoloğu ve kardiovaskuler cerrahi tarafından, anomalinin türü ve varsa eşlik eden ek yapısal anomalilerle ilgili ayrıntılı bir danışmanlık verilerek vakaların prognozu ve gebeliğin yönetiminde izlenebilecek seçenekler hakkında detaylı bilgilendirilme yapılmıştır. Her vaka özelinde ailelere eşlik edebilecek kromozomal anomali varlığının değerlendirilebilmesi için, fetal hafta göz önüne alınarak, koryon villüs örneklemesi, amniosentez, veya kordosentez seçeneklerinden biri önerilmiştir. İnvaziv tanı testini kabul eden ailelere test yapılıp sonucuna göre aileler tekrar bilgilendirilmiştir. Multidisipliner bir danışmanlık sonucunda gebelik terminasyonu tercih eden ailelerde gebelik termine edilmiştir. Canlı doğan fetusların hepsinde postnatal dönemde fetal ekokardiyografi yapılıp tanı kesinleştirilmiş ve bu hastalar çalışmaya dahil edilmiştir.

Çalışmamız verilerinin istatistiksel analizi için SPSS Versiyon 25 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, ABD) kullanıldı. İstatistiksel verilerde ortalama standart sapma, medyan değer (minimum-maksimum değer) ve sayı (yüzde oran) olarak verildi.

RESULTS

Çalışma süreci içinde toplamda 93 olgunun prenatal dönem konotrunkal kalp anomali tanısı mevcuttu, ancak bu vakalardan 14 tanesi takipten çıkma, postnatal verilerine ulaşamama veya postnatal dönemde konotrunkal kalp anomali tanısının doğrulanmaması gibi sebeplerle analiz edilmedi ve çalışmamızı 79 vakayı analiz ederek gerçekleştirdik. Çalışmaya aldığımız 79 vakanın ortalama maternal yaşı 30.2 idi. Hastaların refere kliniğimize başvurduğu ortalama gebelik haftası 27.5 olarak hesaplandı. En sık izlenen konotrunkal kalp anomalisi Fallot tetralojisiydi (40.5%). Olgulardan 21 tanesi büyük arter transpozisyonu (26.5 %), 20 tanesi çift çıkışlı sağ ventrikül (25.3 %) ve 6 tanesi de trunkus arteriozus (7.5%) olarak tanı almıştı (Tablo 1).

Tablo 1: Demografik özellikler ve konotrunkal anomalinin tipine göre vakaların dağılımı

Prenatal konotrunkal kalp anomalisi tanısı alan fetus sayısı §V	79
Maternal yaş (yıl)*	**30.2 ± 4.9**
Gravida #	**2 (1-7)**
Parite #	**1 (0-5)**
Hastanemize başvuru haftası*	**27.5 ± 6.6**
Fallot Tetralojisi (FT) §	**32 (40.5%)**
Büyük Arter Transpozisyonu (BAT) §	**21 (26.5%)**
Çift Çıkışlı Sağ Ventrikül (ÇÇSV) §	**20 (25.3%)**
Trunkus Arteriozus (TA) §	**6 (7.5%)**

***: Ortalama ± SD**

#: Ortanca (min-mak)

§: Sayı (%)

Gebelik sonuçlarını incelediğimizde 79 vakadan 9'nda (11.4%) gebelik terminasyon ile sonuçlanmıştır. Bir olguda (BAT tanılı) intrauterin fetal ölüm gerçekleşmiştir. Altmış dokuz (87.3 %) hastanın gebeliği canlı doğum ile sonuçlanmıştır. Konotrunkal anomalinin tipine göre gebelik sonuçları Tablo 2 de gösterilmiştir. Hastaların 33 (41.7%) tanesinde konotrunkal anomaliye ek ekstrakardiyak yapısal anomali mevcuttu. Ekstrakardiyak yapısal anomali bulunma oranı en yüksek trunkus arteriozus tanılı hasta grubu (TA tanılı hastaların 83.3%), ikinci sırada ise çift çıkışlı sağ ventrikul tanılı hasta grubuydu (ÇÇSV tanılı hastaların 55%'de). Ekstrakardiyak yapısal anomali oranı en düşük grup ise büyük arter transpozisyon tanılı hastalardı (BAT tanılı hastaların 23.8%). Yetmiş dokuz hastadan 32 (40.5%) tanesine prenatal invaziv tanı testi uygulanmıştı ve 15 hastada kromozomal anomali saptandı. Prenatal invaziv tanı testi yapılan hastalar içinde, en yüksek kromozomal anomali saptanma oranı trunkus artriozus tanılı hasta grubunda ((100%) 3/3), en düşük kromozomal anomali saptanma oranı ise büyük arter transpozisyon tanılı hasta grubunda izlendi ((25%)-1/4) (Tablo2).

Tablo 2: Konotrunkal anomalinin tipine göre gebelik sonuçları

	FT (n:32)	BAT (n:21)	ÇÇSV (n:20)	TA (n:6)	Toplam(79)
Gebeliğin terminasyonu	**3 (9.3%)**	**2 (9.5%)**	**4 (20%)**	**0**	**9 (11.4%)**
Fetal ölüm	**0**	**1 (4.7%)**	**0**	**0**	**1 (1.2%)**
Canlı doğum	**29 (90.6%)**	**18 (85.7%)**	**16 (80%)**	**6 (100%)**	**69 (87.3%)**
Ek ekstrakardiyak yapısal anomali varlığı	**12 (37.5%)**	**5 (23.8%)**	**11 (55%)**	**5 (83.3%)**	**33 (41,7%)**

Prenatal invaziv tanı testi varlığı	**14 (43.7%)**	**4 (19.0%)**	**11 (55%)**	**3 (50%)**	**32 (40,5%)**
Kromozomal anomali varlığı	**5 (15.6%)**	**1 (4.7%)**	**6 (30%)**	**3 (50%)**	**15 (18.9%)**

En sık izlenen kromozomal anomali Trizomi 21 (6/15), ikinci sık izlenen ise Trizomi 18 di (5/15). Kromozomal anomali saptanan Fallot tanılı 5 hastadan 4'ünde tanı Trizomi 21 di. Kromozomal anomali saptanan çift çıkışlı sağ ventrikül tanılı 6 hastadan 2'nde tanı Trizomi 21, 3 hastada ise tanı Trizomi 18 di. Kromozomal anomali saptanan Trunkus arteriozus tanılı 3 hastadan 2'nde tanı DiGeorge olarak tespit edildi. Büyük arter transpozisyon tanısı olup kromozomal anomali tespit edilen tek vakada tanı Trizomi 18'di. (Bu vakaya eşlik eden multisistem ekstra kardiyak anomalilerde mevcuttu) (Tablo3).

Tablo 3: Konotrunkal anomalinin tipine göre saptanan kromozomal anomaliler

	FT(n:5)	BAT(n:1)	ÇÇSV(n:6)	TA(n:3)	Toplam(n:15)
Trizomi 21	**4(%80)**	-	**2(%33)**	-	**6 (%40)**
Trizomi 18	-	**1(%100)**	**3(%50)**	**1(%33)**	**5 (%33.4)**
DiGeorge	-	-	-	**2(%66)**	**2 (%13.3)**
Del 2q37.3	-	-	**1(%17)**	-	**1 (%6.6)**
Dup 3p del 4q	**1(%20)**	-	-	-	**1 (%6.6)**

n: sayı (%)

Canlı doğan 69 vakayı incelediğimizde ortalama doğum haftasının 37, ortalama doğum kilosunun 2797 gram, 5. dakika APGAR skorunun ortalama 8 ve 38 (55.07%) tanesinin cinsiyetinin erkek olduğunu saptadık, vakaların 26 tanesi yenidoğan döneminde eks oldu (Tablo 4).

Tablo 4: Canlı doğan vakaların özellikleri (n:69)

Doğum haftası*	37.05 ± 2.2
Doğum Kilosu*	**2797.89 ± 652**
Apgar 5.dakika #	**8 (1-9)**
Cinsiyet (erkek) §	**38 (55.07%)**
Yenidoğan döneminde sağkalım §	**43 (62.3%)**

***: Ortalama ± SD**

#: Ortanca (min-mak)

§: Sayı (%)

Konotrunkal anomalinin izole veya non izole olmasına göre gebelik sonucuna baktığımızda, gebeliği terminasyon ile sonuçlanan 9 hastadan 8 inin non izole konotrunkal anomali tanısı mevcuttu. Ayrıca canlı doğan 69 vakadan 41'nde izole konotrunkal anomali tanısı mevcuttu (Tablo 5).

Toplam vaka sayısı (n:79)	İzole vakalar (n:43)	Non izole vakalar (Ekstrakardiyak ve/veya kromozomal anomali varlığı) (n:36)
Gebeliğin terminasyonu	**1 (2.3%)**	**8 (22.2%)**
Fetal ölüm	**1 (2.3%)**	**0**
Canlı doğum	**41 (95.3%)**	**28 (77.7%)**

n: sayı (%)

TARTIŞMA

Konotrunkal kalp anomalileri hem erken tedavi gereksinimi hem de postnatal erken dönem siyanotik doğumsal kalp hastalıklarının önemli bir kısmını oluşturması sebebiyle ciddi önem arz etmektedir (9).

Konotrunkal anomali tanımında aort ve pulmoner arter çıkış anomalileri tanımlandığından, prenatal tanının ve sonucunda erken müdahalenin bu anomalilerde postnatal hipoksi ve morbiditeyi azalttığı literatürde bildirilmiştir (8). Konotrunkal anomalileri önemli kılan bir diğer durum ise doğru prenatal tanı alabilme oranının diğer konjenital kalp hastalıklarına kıyasla düşük olmasıdır. Literatürde prenatal tanı oranı %40-70 arasında bildirilmektedir (10,11). Bunun temel nedeni, ikinci trimester rutin ultrasonografik anatomik taramada fetal kalbin büyük oranda sadece 4 oda kesiti ile değerlendirilmesi olabilir. Fetal kalp incelemesine 4 oda kesitine ek olarak sağ-sol ventrikül çıkış yolları dahil edilmediğinde konotrunkal anomalilerin prenatal dönemde tanı almama olasılığı çok yükselmektedir. Kliniğimiz gibi deneyimli perinatoloji merkezlerinde konotrunkal anomalilerin prenatal tanısı yüksek doğrulukla konulabilmektedir.

Çalışmamızda vakaların konotrunkal anomalinin tipine göre dağılımına baktığımızda en çok Fallot tetralojisi (40.5%) vakası, daha sonra benzer sayıda çift çıkışlı sağ ventrikül (25.3%) ve büyük arter transpozisyonu (26.5%) vakası şeklinde dağılım gösterdiğini tespit ettik, bu vaka dağılımının geniş serili literatür ile uyumlu olduğunu gözlemledik (12,13). Ancak ülkemizde Kaya ve ark. yaptığı çalışmada konotrunkal anomaliler grubu içinde çift çıkışlı sağ ventrikül tanı oranının en yüksek olduğu bildirilmiştir (14). Bizim serimizdeki vaka dağılımının yurt dışı verileri ve güncel literatürle uyumlu olduğunu tespit ettik.

Gebelik sonuçları açısından çalışmamızı değerlendirdiğimizde sadece 9 (11.4%) hastada gebelik terminasyonu gerçekleştirildiğini saptadık. Bu sayı gerek yurt dışı verileri gerekse ülkemizde yapılan çalışmalara göre oldukça az olarak göze çarpmaktadır (13,14). Biz bunun sebebini refere merkez olan kliniğimizin bulunduğu bölgedeki toplumun dini ve kültürel inanışının gebelik terminasyon seçeneğine sıcak bakmamasına bağladık. 1 vakamızda fetal ölüm gerçekleşti ve çalışmamızda 69 fetus canlı olarak doğdu. Konotrunkal kalp anomalilerine ekstrakardiyak anomali eşlik etme oranı açısından literatürü taradığımızda, bu oranın %25-40 aralığında olduğunu saptadık (14-17). Bizim çalışmamızda da konotrunkal anomalilere ek ekstrakardiyak anomali eşlik etme oranı benzer şekilde 41.7% olarak bulundu ve bu bulgumuz üst sınırda da olsa literatür ile uyumluydu. Çalışmamızda dikkat çeken başka bir bulgu ise serimizdeki trunkus arteriozus vakalarının literatüre kıyasla ekstrakardiyak ve kromozomal anomaliler ile daha yüksek oranda ilişkili olduğunu saptamamızdır. Ancak trunkus arteriozus tanılı vaka sayımızın azlığı nedeniyle bu bulgu hakkında ek bir yorumda bulunamadık. Serimizde kromozomal anomali tanısı için 79 hastanın 32(40.5%) tanesine invaziv tanı testi uygulanmıştı ve kromozomal anomali oranımız %18.9 olarak saptandı. Bu oran literatürle uyumlu olmakla beraber alt sınırda görülmektedir (14,16,17). Bunun nedeninin görece olarak daha az oranda hastaya prenatal tanı testi uygulamamız olduğunu düşünmekteyiz. Ayrıca konotrunkal anomalileri tiplerine göre ayrıntılı ince-

lediğimizde kromozomal anomali eşlik etme oranını en yüksek trunkus arteriozus ikinci sırada ise çift çıkışlı sağ ventrikül tanılı hastalarda tespit ettik. Çok geniş serilerle yapılan 2 çalışmada da çift çıkışlı sağ ventrikül tanısı varlığında kromozomal anomali eşlik etme oranı Fallot tetralojisine kıyasla daha yüksek bulunmuştur, en düşük kromozomal anomali eşlik etme oranının ise büyük arter transpozisyon tanısı varlığında izlendiği belirtilmiştir (12,18). Bizim çalışmamızda bu bulguları desteklemekle beraber, Fallot tetralojisi tanısına kromozomal anomali eşlik etme oranı bizim çalışmamızda literatüre kıyasla biraz daha düşük tespit edildi. (12,14-18). Çalışmamızda Fallot tetraloji tanısı varlığında literatüre göre daha az kromozomal anomali oranı saptanmasının nedenini bu grupta ekstrakardiyak anomali eşlik etme oranınında biraz daha az olmasına bağlamaktayız. Ayrıca anomaliler özelinde baktığımızda çift çıkışlı sağ ventrikül tanısı varlığında en sık eşlik eden kromozomal anomalinin Trizomi 18 olması, Fallot tetralojisi tanısına ise en sık Trizomi 21'in eşlik etmesi literatürle uyumlu olarak bulunmuştur (12,14,18).

Canlı doğan vakaları değerlendirdiğimizde, doğum haftasının, doğum kilosunun ve özellikle yenidoğan döneminde hayatta kalan bebek oranını (62.3%) yüksek vaka sayılı serilerde verilmiş olan %40 ile %70 arası oranlarla karşılaştırdığımızda üst sınıra yakın olduğunu saptadık (14-19). Bu sonucu da kliniğimizin yenidoğan biriminin de tersiyer merkez olması ve prenatal tanı ile erken müdahale şansının yakalanmasına bağlamaktayız. Son olarak vaka serimizde beklenildiği gibi, konotrunkal kalp anomalisinin izole olduğu vakalarda canlı doğum oranının daha yüksek, ekstrakardiyak anomali ve/veya kromozomal anomalisi olan vakalarda gebelik terminasyon oranının daha yüksek olduğunu saptadık. Bu sonucun literatürle uyumlu olduğunu ve beklenilen bir sonuç olduğunu söyleyebiliriz (14-19).

Çalışmamızın retrospektif bir çalışma olması limitasyonu olarak değerlendirilebilir. Ancak kliniğimizin refere bir merkez olması, prenatal tanının deneyimli perinatologlar tarafından konması ayrıca tüm vakaların tanısının postnatal ekokardiyografi ile kesinleştirilmesi çalışmamızın güçlü yönleri olarak sayılabilir.

Sonuç olarak konotrunkal kalp anomalilerinin konjenital kalp hastalıkları içinde önemli bir orana sahip olması, rutin anatomik taramada tanısının zor olması ve prenatal tanının erken postnatal dönemde girişim ve tedavi şansı vermesi nedeniyle prenatal doğru tanının çok ciddi öneme sahip olduğunu ve bu sayede fetusların sekelsiz hayatta kalma şansının arttığına inanmaktayız. Ayrıca ekstrakardiyak anomali ya da kromozomal anomali eşlik ettiğinde gebeliğin terminasyonu veya takip seçeneğinin multidisipliner birimlerden oluşan konsey kararıyla referans merkezlerce ailelere ayrıntılı ve iyi bir bilgilendirme ile sağlanabileceği ve bu şekilde bilgilendirmenin çok önemli olduğu kanısındayız.

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Maternal Behçet Hastalığının Fetal Adrenal Bez Boyutlarına Etkisi

The Effect of Maternal Behçet's Disease on Fetal Adrenal Gland Sizes

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ÖZ

Amaç: Maternal Behçet Hastalığı (BH) ile komplike gebeliklerde artmış inflamasyonun fetal adrenal bezin erken olgunlaşmasına neden olabileceğini, dolayısıyla fetal adrenal bez boyutunun değişebileceğini hipoteze ederek, maternal BH'li gebeliklerde fetal adrenal bez boyutlarını incelemeyi amaçladık.

Gereç ve Yöntemler: Kesitsel tasarımda ki bu çalışma, Mayıs 2022-Mayıs 2023 tarihleri arasında Ankara Şehir Hastanesi perinatoloji kliniğinde yürütüldü. Çalışmaya 31-34 gebelik haftalarında başvuran BH tanısı almış 21 gebe ve gebelik yaşı vaka grubu ile eşleştirilmiş ve rastgele seçilmiş 63 sağlıklı gebe dahil edildi. Her iki adrenal bez ile adrenal bezin fetal zonunun genişliği ve uzunluğu transvers kesitte ölçülerek uzunluk x genişlik x π formülü ile transvers adrenal alan (TAA), transvers fetal zon alanı (FZA) ve fetal zon alanının transvers adrenal alana oranı (FZA/TAA) hesaplandı. Vaka ve kontrol grupları arasında ayrıca atak geçiren ve geçirmeyen BH alt gruplarında fetal adrenal ölçümler karşılaştırıldı.

Bulgular: Sol adrenal bezde toplam adrenal genişlik, TAA, fetal zon genişlik ve FZA vaka grubunda anlamlı olarak yüksek bulundu. Ayrıca sol FZA/TAA oranı vaka grubunda istatistiksel olarak anlamlı oranda yüksek saptandı. Sağ adrenal bezde ise fetal zon genişliği, FZA ve FZA/TAA oranı vaka grubunda anlamlı oranda yüksek izlendi. Ayrıca atak geçiren grupta sol adrenal bezde fetal zon genişliği, FZA ve FZA/TAA oranı anlamlı ölçüde yüksek ve sağ adrenal bezde ise toplam adrenal uzunluk, TAA, fetal zon genişliği ve FZA istatiksel olarak anlamlı oranda yüksek izlendi.

Sonuç: Maternal BH ile komplike gebeliklerde fetal adrenal bez boyutları etkilenebilmektedir. Bu etkinin daha çok adrenal bezin fetal zon bölümünde olduğu ve gebeliğinde atak geçiren grupta daha belirgin olduğu görülmektedir. BH gebeliklerinde artmış inflamasyon ve sitokin seviyeleri nedeniyle intrauterin strese maruz kalan fetuslarda adrenal bezin daha erken matürasyonu söz konusu olabilir.

Anahtar Kelimeler: Behçet Hastalığı, fetal adrenal bez boyutları, inflamasyon, vaskülit.

ABSTRACT

Aim: We aimed to investigate fetal adrenal gland sizes in pregnancies with maternal Behçet's Disease (BD), hypothesizing that increased inflammation in pregnancies complicated with maternal BD may cause premature maturation of the fetal adrenal gland, and therefore fetal adrenal gland size may change.

Materials and Methods: This cross-sectional study was carried out between May 2022 and May 2023 in Ankara City Hospital perinatology clinic. Twenty-one pregnant women with BD at 31-34 weeks of gestation and 63 randomly selected healthy pregnant women whose gestational age were matched with the case group were included in the study. Transverse adrenal area (TAA), transverse fetal zone area (FZA) and the ratio of fetal zone area to transverse adrenal area (FZA/TAA) were calculated using the formula length x width x π by measuring the width and length of the fetal zone with both adrenal glands. Fetal adrenal measurements were compared between the case and control groups, as well as in the BD subgroups with and without exacerbation.

Results: Total adrenal width, TAA, fetal zone width and FZA in the left adrenal gland were significantly higher in the case group. The left FZA/TAA ratio was found to be statistically significantly higher in the case group. In the right adrenal gland, fetal zone width, FZA and FZA/TAA ratios were significantly higher in the case group. In addition, fetal zone width, FZA and FZA/TAA ratios were significantly higher in the left adrenal gland, and total adrenal length, TAA, fetal zone width and FZA were statistically significantly higher in the right adrenal gland in the exacerbated group.

Conclusion: Fetal adrenal gland dimensions may be affected in pregnancies complicated by maternal BD. This effect is seen mostly in the fetal zone of the adrenal gland and is more prominent in the group who had an attack during pregnancy. Fetuses exposed to intrauterine stress due to increased inflammation and cytokine levels in BD pregnancies may have earlier maturation of the adrenal gland.

Keywords: Behçet's Disease, fetal adrenal gland dimensions, inflammation, vasculitis.

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GİRİŞ

Behçet Hastalığı (BH), 1937 yılında Prof. Dr. Hulusi Behçet tarafından tanımlanmış olup, tekrarlayan oral aftöz ülserler, genital ülserler ve oküler inflamatuar lezyonlar ile karakterize, multisistemik inflamatuar bir vaskülittir. (1). Hastalığın prevalansı coğrafi olarak değişken olup, Orta Doğu ve Uzak Doğu'daki insanları daha sık etkilemektedir. Hastalığın en yaygın görüldüğü Türkiye'de ise sıklığı 3/1000 civarındadır. Patogenezi tam olarak açıklanamamakla birlikte genetik olarak yatkın bireylerde, enfeksiyöz ajanlar gibi tetikleyici faktörler tarafından başlatılan otoimmün bir reaksiyon ile geliştiği bildirilmektedir (2, 3). BH için tanı değeri olan bir laboratuvar incelemesi yoktur, bu nedenle tanısı klinik bulgular ile konur (4). BH tanısı, 1990 Uluslararası Behçet Hastalığı Çalışma Grubu Kriterlerine göre oral ülserasyona eşlik eden genital ülserler, üveit veya retinal vaskülit gibi göz lezyonları, eritema nodozum ve psödofollikülit benzeri cilt lezyonları veya pozitif bir paterji testi bulgularından herhangi ikisinin varlığı ile konmaktadır (5). BH'de görülen vaskülit daha çok küçük damar tutulumu şeklinde olup immün-kompleksler aracılığı ile gerçekleşir. Yüzeyel ve derin ven trombozu da BH'de yaygın olarak görülmektedir.

Gebelik çeşitli hormonal, metabolik, immünolojik, fizyolojik ve vasküler değişikliklere neden olan ve çoğu sistemi etkileyen fizyolojik bir durumdur. Farklı ülkelerden yapılan çalışmalar, gebeliğin BH seyri üzerindeki etkisinin hastalar arasında ve hatta aynı hastada farklı gebelikler sırasında değişken olduğunu göstermektedir (6-8). BH plasental damarları etkileyerek fetal ve obstetrik komplikasyonlara yol açabilmektedir. Plasentada desidual vaskulit ve necrotizan villitise neden olarak, immün-komplekslerin sebep olduğu hiperkoagulopati ve trombüs formasyonu ile fetal gelişme kısıtlılığı (FGK) ve preterm doğum gibi obstetrik komplikasyonlara neden olabildiği gösterilmiştir (9, 10). Özellikle hastalığın aktif döneminde gebe kalan ya da gebelikte hastalığı alevlenen hastalarda fetal etkilenmenin ve obstetrik komplikasyonların daha sık gözlendiği bildirilmiştir (11).

Fetal adrenal bezler, fetusun gelişimi, olgunlaşması, neonatal yaşama adaptasyonu ve hipoksi, intrauterin enfeksiyonlar, inflamasyonlar veya cerrahi gibi nedenlerle oluşan intrauterin strese karşı mücadele edebilmesinde kritik öneme sahip endokrin organlardır (12). İntrauterin strese neden olabilecek herhangi bir faktörün varlığında fetal adrenal kan akımında redistribüsyon ve adrenal bez boyutlarında değişikliğe sebep olabileceği çeşitli çalışmalarda gösterilmiştir (13-18). Ayrıca, sitokinlerin ve inflamasyonun yüksek seviyelerinin, hipotalamus-hipofiz-adrenal (HPA) aksını aktive ederek fetal adrenal bez fonksiyonunu ve boyutlarını etkilediği de bildirilmiştir (19-21).

BH'li gebeliklerde artmış inflamasyonun fetal adrenal bezin erken olgunlaşmasına neden olabileceğini, dolayısıyla BH'li gebeliklerde fetal adrenal bez boyutunun değişebileceğini düşünüyoruz. Çalışmamızda maternal Behçet Hastalığı olan gebeliklerde fetal adrenal bez boyutlarını incelemeyi amaçladık.

GEREÇ-YÖNTEM

Kesitsel tasarımda ki bu çalışma, Mayıs 2022-Mayıs 2023 tarihleri arasında Ankara Şehir Hastanesi perinatoloji kliniğinde yürütüldü. Çalışmaya 31-34 gebelik haftalarında başvuran BH tanısı almış 21 gebe ve gebelik yaşı vaka grubu ile eşleştirilmiş ve rastgele seçilmiş 63 sağlıklı gebe dahil edildi. Araştırma protokolü, çalışmaya başlamadan önce Ankara Şehir Hastanesi Kurumsal Etik Kurulu bölümü tarafından onaylandı (E2-22-2140). Tüm katılımcılardan bilgilendirilmiş yazılı onam alındı.

Gebeliklerin gebelik yaşı son adet tarihine göre belirlendi ve gebeliğin 9+0 ile 13+6 haftaları arasında baş-popo uzunluğu (CRL) ölçümü ile doğrulandı. Maternal yaş, gebelik öncesi vücut kitle indeksi (VKİ), obstetrik öykü, otoimmün hastalık süresi, kullanılan ilaçlar, gebelikte atak geçiren hasta sayısı, ultrasonografik incelemenin yapıldığı gebelik haftası bilgileri kaydedildi. Fetal anomali, FGK, preterm prematüre membran rüptürü (PPROM), çoğul gebelik, gestasyonel diabetes mellitus, sigara kullanımı, preeklampsi ve diğer maternal sistemik hastalık tanılı gebeler çalışma dışı bırakıldı.

Tüm fetal ultrasonografik inceleme, Voluson E8'in (GE Healthcare, Milwaukee, WI) 4-8 MHz konveks ultrason probu kullanılarak, hastanın vaka veya kontrol grubundan olduğunu bilmeyen tek bir perinatoloji uzmanı (DUH) tarafından yapıldı. Fetal anomali taraması, biyometrik ölçümler ve fetal iyilik halinin değerlendirilmesinden sonra fetal adrenal bez boyutları ölçüldü. Ultrason probu fetal abdominal çevre kesitinden kaudal olarak kaydırıldığında, vertebranın her iki yanında böbreğin üst polünü çevreleyen sağ ve sol fetal adrenal bezin transvers kesiti görüntülendi. Görüntü büyütülerek, ortadaki hiperekoik fetal zon ile onu çevreleyen hipoekoik korteks arasındaki ayrım netleştirildi. Her iki adrenal bezin ve fetal zonun genişliği ve uzunluğu iki eksende ayrı ayrı ölçüldü (Resim 1). Kostal veya vertebral kemiklerin akustik gölgesi nedeniyle fetal adrenal yüksekliği ölçmek her hastada mümkün olamadığından, çalışmamızda fetal adrenal volümü ölçmek yerine, uzunluk x genişlik x π formülü ile transvers adrenal alan (TAA) hesaplandı. Aynı formül fetal zon boyutları için de kullanılarak transvers fetal zon alanı (FZA) ve fetal zon alanının transvers adrenal alana oranı (FZA/TAA) hesaplandı. Tüm ölçümler her hasta için iki kez tekrarlandı ve ortalaması kaydedildi.

İstatistiksel Analizler

Numune büyüklüğü G Power yazılımı kullanılarak analiz edildi ((versiyon 3.1; Franz Foul, Universitat Kiel, Kiel, Almanya) (22). Örneklem büyüklüğü için, p-değeri 0.05 ve %80'lik bir güç ile 0.80'lik bir etki büyüklüğü belirlendi. Bu şekilde her grupta en az 17 vaka olması gerektiği sonucuna varılmış ve her vaka için 3 kontrol alınması planlanmıştır. Social Sciences (SPSS), yazılım versiyonu 17.0 (SPSS Inc, Chicago, IL) kullanılarak yapıldı. Tanımlayıcı istatistikler normal dağılıma sahip sayısal veriler için ortalama ± standart sapma veya veya normal bir dağılım izlemeyen sayısal veriler için medyan (IQR'ler (Çeyrekler Arası Aralıklar)) değerleri olarak verildi. İki bağımsız grubun değerlerinin karşılaştırılmasında normal dağılan değişkenler için " Independent t-testi ", normal dağılmayan değişkenler için " Mann-Whitney U testi " kullanıldı. Sol ve sağ FZA'nın gruplar arasında ki dağılımı Şekil 1'de hata çubuğu (error bar) ile gösterilmiştir. Gebeliğinde atak geçiren ve geçirmeyen BH grupları arasında FZA ölçümlerinin dağılımı boxplot kutu grafiği ile Şekil 2'de gösterildi. Kutu, çeyrekler arası aralığı tanımlar ve kutunun ortasındaki çizgi medyanı sembolize eder. Çalışmadaki .05'in altındaki tüm p değerleri anlamlı olarak kabul edilmiştir.

BULGULAR

Çalışmamıza maternal Behçet Hastalığı olan 21 gebe ve maternal özelikleri ve gebelik haftaları vaka grubu ile eşleştirilmiş 63 sağlıklı gebe dahil edildi. Maternal yaş, gravide, parite, gebelik öncesi VKI ve ultrasonografik değerlendirmenin yapıldığı gebelik haftaları her iki grupta benzerdi (Tablo 1). Fetal adrenal bez boyutları gebelik haftası ilerledikçe arttığından, biz her iki grupta ultrasonografinin yapıldığı gebelik haftasını 31. ile 34. gebelik haftaları arasında sınırladık.

Tablo 1: Vaka ve kontrol grupları arasında demografik özellikler ve fetal adrenal bez boyutlarının karşılaştırılması

	Vaka grubu (n=21)	Kontrol grubu (n=63)	p değeri
Yaş	27±7	28±5	.177*
Gravide	3±2	2±1	.645*
Parite	1 (0-2)	1 (0-1)	.506†
VKI (kg/m)	28±5	29±4	.458*
Gebelik haftası	32±1	33±1	.226*
Sol TAG (cm)	1.13±0.1	1.01±0.16	**<.001***
Sol TAU (cm)	2.14±0.15	2.13±0.28	.859*
Sol TAA (cm^2)	7.64±0.93	6.81±1.49	**.018***
Sol FZG (cm)	0.68±0.1	0.5±0.17	**<.001***
Sol FZU (cm)	1.34±0.18	1.34±0.25	.994*
Sol FZA (cm^2)	2.86±0.6	2.10±0.75	**<.001***
Sol FZA/TAA	0.38±0.07	0.31±0.09	**.004***
Sağ TAG (cm)	1.02±0.12	1.01±0.16	.754*
Sağ TAU (cm)	2.11±0.18	2.07±0.25	.604*
Sağ TAA (cm^2)	6.76±1.03	6.59±1.38	.608*
Sağ FZG (cm)	0.65±0.12	0.50±0.16	**<.001***
Sağ FZU (cm)	1.29±0.2	1.27±0.24	.729*
Sağ FZA (cm^2)	2.63±0.66	1.98±0.65	**<.001***
Sağ FZA/TAA	0.39±0.08	0.30±0.09	**<.001***

Değerler ortalama ± standart sapma ve ortanca (çeyrekler arası yüzde) olarak verildi. İstatistiksel olarak anlamlı olan sonuçlar koyu renkte gösterildi.

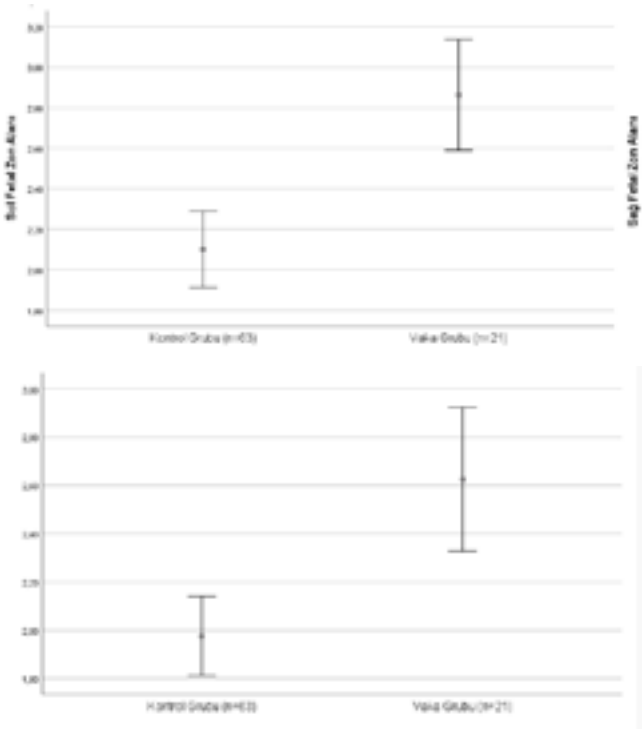
*Bağımsız örneklem T testi

† Mann Whitney U testi

BH grubunda atak geçiren altı hastanın ikisinde düşük doz kortikosteroid tedavisi ve toplam sekiz hastada ise kolşisin tedavisi uygulandı.

Fetal adrenal bez boyutları sağ ve sol adrenal bez de değişkenlik gösterebildiğinden her iki adrenal bez boyutları ayrı ayrı ölçülerek kaydedildi (Tablo 1). Sol adrenal bezde toplam adrenal genişlik, TAA, fetal zon genişlik ve FZA vaka grubunda anlamlı olarak yüksek bulundu. Ayrıca sol FZA/TAA oranı vaka grubunda istatistiksel olarak anlamlı oranda yüksek saptandı. Sağ adrenal bezde ise fetal zon genişliği, FZA ve FZA/TAA oranı vaka grubunda anlamlı oranda yüksek izlendi. Sol ve sağ FZA'nın gruplar arasında ki dağılımı Şekil 1'de gösterilmiştir.

Şekil 1: Vaka ve kontrol gruplarında sol ve sağ fetal zon alanı ölçümlerinin dağılımı



BH grubunda gebeliğinde atak geçiren hasta sayısı altı atak geçirmeyen hasta sayısı ise 15 idi. Atak geçiren ve geçirmeyen grupta da adrenal bez boyutları karşılaştırıldı (Tablo 2).

Tablo 2: Atak geçiren ve geçirmeyen BH alt grupları arasında fetal adrenal bez boyutlarının karşılaştırılması

	Atak + (n=6)	Atak- (n=15)	p değeri
Gebelik haftası	32 (32-33)	33 (31-34)	.717†
Sol TAG (cm)	1.17 (1.12-1.2)	1.16 (1-1.21)	.845†
Sol TAU (cm)	2.22 (2.15-2.32)	2.12 (2-2.21)	.055†
Sol TAA (cm^2)	8.04 (7.83-8.43)	7.46 (6.66-8.4)	.276†
Sol FZG (cm)	0.77 (0.73-0.77)	0.67 (0.59-0.69)	**.004†**
Sol FZU (cm)	1.38 (1.32-1.65)	1.30 (1.21-1.36)	.149†
Sol FZA (cm^2)	3.26 (3.15-3.99)	2.65 (2.51-2.95)	**.008†**
Sol FZA/TAA	0.42 (0.38-0.5)	0.36 (0.30-0.41)	**.043†**
Sağ TAG (cm)	1.14 (0.98-1.18)	0.98 (0.90-1.07)	.065†
Sağ TAU (cm)	2.22 (2.15-2.22)	2.10 (2-2.15)	**.035†**
Sağ TAA (cm^2)	7.9 (6.83-8.19)	6.62 (5.72-7.16)	**.022†**
Sağ FZG (cm)	0.75 (0.68-0.77)	0.64 (0.54-0.67)	**.008†**
Sağ FZU (cm)	1.38 (1.14-1.65)	1.29 (1.12-1.34)	.172†
Sağ FZA (cm^2)	3.21 (2.79-3.52)	2.39 (2.2-2.59)	**.008†**
Sağ FZA/TAA	0.43 (0.36-0.46)	0.36 (0.31-.45)	.186†

Değerler ortanca (çeyrekler arası yüzde) olarak verildi.

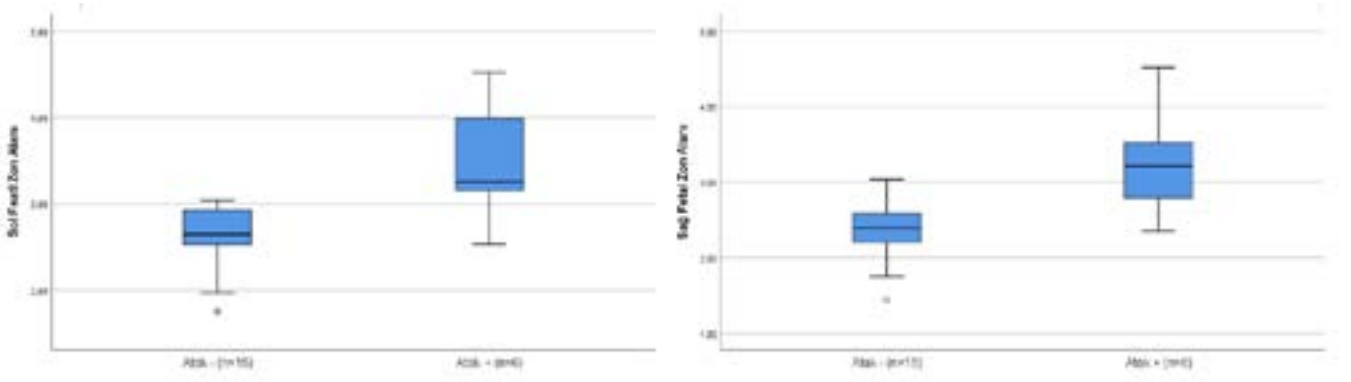
İstatistiksel olarak anlamlı olan sonuçlar koyu renkte gösterildi.

† Mann Whitney U testi

Kısaltmalar: VKI, vücut kitle indeksi; TAG, toplam adrenal genişlik; TAU, toplam adrenal uzunluk; TAA, transvers adrenal alan; FZG, fetal zon genişlik; FZU, fetal zon uzunluk; FZA, fetal zon alanı.

Atak geçiren grupta sol adrenal bezde fetal zon genişliği, FZA ve FZA/TAA oranı anlamlı ölçüde yüksek ve sağ adrenal bezde ise toplam adrenal uzunluk, TAA, fetal zon genişliği ve FZA istatiksel olarak anlamlı oranda yüksek izlendi. Gebeliğinde atak geçiren ve geçirmeyen BH grupları arasında FZA ölçümlerinin dağılımı Şekil 2'de gösterilmiştir.

Şekil 2: Atak geçiren ve geçirmeyen BH alt grupları arasında sol ve sağ fetal zon alanı ölçümlerinin dağılımı



TARTIŞMA

Çalışmamızda BH'de artan nötrofil fonksiyonları ve oksidatif doku hasarından sorumlu olabilecek reaktif oksijen türlerinin (ROS) aşırı üretimi, immünolojik değişiklikler, T lenfosit alt gruplarında ve fonksiyonlarında ki anormalliklerin BH ile komplike gebeliklerde fetal HPA aksını aktive ederek fetal adrenal bez boyutlarında değişikliklere sebep olabileceğini hipoteze ettik ve fetal adrenal bez boyutlarını incelemeyi amaçladık. İntrauterin strese yol açabilecek herhangi bir nedenin fetüste bazı kompansatuar mekanizmaların aktivasyonuna yol açtığı bilinmektedir (23, 24). Fetus stres durumunda öncelikle hayati organları korumak için beyne, kalbe ve adrenal bezlere kan akışını artırarak bu strese yanıt verirken, diğer yandan da HPA aksını uyararak fetal adrenal steroidogenezi aktive eder (19). Tüm bu kompansatuar mekanizmalar fetal adrenal bezin erken matürasyonuna sebep olabilmektedir (14).

Çalışmamızda BH ile komplike gebeliklerde fetal adrenal bez boyutlarının etkilenebileceği özellikle bu etkilenmenin daha çok adrenal bezin fetal zon kısmında gerçekleştiği gösterildi. Her iki adrenal bezde fetal zon genişliği ve FZA'nın anlamlı oranda arttığı görüldü. FZA/TAA oranında da istatiksel olarak anlamlı oranda artış izlendi ve bu oranın artması adrenal bezdeki büyümenin daha çok fetal zondaki büyümeden kaynaklandığını düşündürdü. Ayrıca gebelik döneminde atak geçiren aktif BH gebeliklerinde fetal adrenal bez boyutlarında özellikle FZA'daki artış atak geçirmeyen gruba göre anlamlı oranda daha yüksek saptandı. Fetal zon hipoksi, inflamasyon ve hiperglisemi gibi intrauterin stres sinyallerinin HPA aksına iletilmesiyle aktive olur ve sistemik ihtiyaçlara yanıt olarak glukokortikodleri üreterek artan adrenal kan akımı ile dolaşıma salgılar (25-27). Fetüsün ekstrauterin yaşama hazırlanmasında kritik öneme sahip olan glukokortikoid, akciğer olgunlaşmasını ve diğer organ sistemlerinin gelişimini destekler ve ayrıca doğumun başlamasında rol oynar (27).

İntraamniyotik ve ekstra amniyotik inflamasyonun fetal HPA aksı üzerindeki etkisini araştıran çalışmalar, proinflamatuar sitokinlerin fetal HPA aksını uyardığını ve böylece fetal adrenal steroidogenezi aktive ettiğini ortaya koymaktadır (19, 28). Preterm doğumla komplike olan gebeliklerde, intraamniyotik inflamasyona maruz kalan fetüslerde adrenal bez hacimlerinin daha yüksek olduğu gösterilmiştir (18). Amniyonit, piyelonefrit veya cinsel yolla bulaşan hastalık gibi maternal enfeksiyonların fetal HPA aksı üzerindeki etkisinin araştırıldığı bir çalışmada maternal enfeksiyona maruz kalan fetuslarda adrenal steroidlerin artmış üretimi saptanmıştır (29). Benzer bir mekanizmayla, biz de BH'de inflamasyon ve artmış sitokin seviyelerinin HPA aksının aktivasyonuna neden olup ve fetal adrenal bez fonksiyonunu ve boyutlarını etkileyebileceğini düşündük.

Fetal adrenal bezin hem preterm hem de term doğumda önemli bir rol oynadığı iyi bilinmektedir. Bu nedenle fetal adrenal bez ultrasonografisinin spontan preterm doğumu öngörmedeki rolü uzun süre araştırılmıştır (16, 17). Adrenal bezin özellikle fetal zon genişliği ölçümünün, yedi gün içinde erken doğum riski taşıyan kadınları belirlemede servikal uzunluktan daha üstün olduğunu gösterilmiştir (16). Başka bir çalışmada ise gebeliğin 22 0/7 ve 30 6/7 haftaları arasında ultrasonografi ile ölçülen fetal adrenal boyutunun, asemptomatik nullipar gebelerde spontan preterm doğum için belirleyici olmadığı gösterilmiştir (17). Ayrıca literatürde FGK, maternal diyabetes mellitus ve intraamniyotik enfeksiyonlar ile komplike gebeliklerde de fetal adrenal bez boyutlarını araştıran birçok çalışma mevcuttur (14, 29-31). FGK olan 110 gebe ve sağlıklı 110 gebeyi içeren kontrol grubu ile yürüttüğümüz çalışmamızda, FGK'nın toplam fetal adrenal bez ve FZ boyutlarında ve adrenal kan akışında önemli bir artışa neden olduğu saptandı (14). Fetal adrenal hacmin tahmini fetal ağırlık, doğum ağırlığı ve maternal leptin ve HbA1c düzeyleri ile ilişkisinin araştırıldığı çalışmada maternal leptin ve HbA1c seviyeleri ile toplam fetal adrenal bez hacmi arasında anlamlı bir pozitif ilişki bulunmuştur (31).

Literatürde fetal adrenal bez boyutlarını inceleyen çalışmalarda adrenal volüm, uzunluk-genişlik-yükseklik ölçümleri veya bizim çalışmamızda olduğu gibi transvers alan ölçümleri kullanılmıştır. İleri gebelik haftalarında sagital veya koronal kesitte kosta gölgelerinin artması sebebiyle adrenal yükseklik ölçümü her zaman mümkün olmayabilir ve görüntülemek fazla zaman gerektirebilir. Bu nedenle biz çalışmamızda adrenal volüm ölçmek yerine klinik uygulaması çok daha pratik olan ve Blue ve ark.'nın da çalışmalarında kullandığı transvers adrenal alan ve fetal zon alanını hesaplayarak bu ölçümleri kullandık (32).

Çalışmamız Behçet Hastalığı gibi otoimmün inflamatuar bir hastalık grubunda fetal adrenal bez boyutlarını araştıran literatürde ki ilk çalışmadır. Ayrıca fetal adrenal bez boyutlarını inceleyen çalışmalar arasında transvers adrenal alan ve fetal zon alan ölçümünü kullanan oldukça az sayıda çalışma vardır. Ancak çalışmamızın kesitsel tasarımda olması ve BH'nin oldukça seyrek görülen bir hastalık olup kısıtlı gebelik haftalarının çalışmaya dahil edilmesi nedeni ile katılımcı sayısının düşük olması çalışmamızın kısıtlı yönleridir. Daha fazla katılımcı ile çok merkezli çalışmalar bu konuda daha fazla bilgi sağlayacaktır.

SONUÇ

Sonuç olarak, maternal Behçet Hastalığı olan gebeliklerde fetal adrenal bez boyutları etkilenebilmektedir. Bu etkinin daha çok adrenal bezin fetal zon bölümünde olduğu ve gebeliğinde atak geçiren grupta daha belirgin olduğu görülmektedir. BH gebeliklerinde artmış inflamasyon ve sitokin seviyeleri nedeniyle intrauterin strese maruz kalan fetuslarda adrenal bezin daha erken matürasyonu söz konusu olabilir. Bu nedenle BH'de intrauterin strese bağlı oluşabilecek fetal ve obstetrik komplikasyonlar açısından dikkatli perinatal takibin yapılması faydalı olacaktır.

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Özgün Araştırma / Original Article

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Gebeliğin intrahepatik kolestazında hastalığın şiddeti ve tedaviye yanıtın perinatal sonuçlara etkisi

The effect of disease severity and response to treatment on perinatal outcomes in intrahepatic cholestasis of pregnancy

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ÖZ

Amaç: Gebeliğin intrahepatik kolestazı (GİHK) ile komplike olan gebeliklerde, serum safra asiti (SA) düzeyleri ve ursodeoksikolik asit (UDKA) tedavisine verilen cevabın perinatal sonuçlar üzerine etkisini araştırmaktır.

Gereçler ve Yöntem: Bu çalışmada Ocak 2013 ile Ocak 2018 tarihleri arasında üçüncü basamak bir merkezde GİHK nedeniyle takip edilen gebelikler retrospektif olarak analiz edildi. GİHK şiddeti, serum SA seviyelerine göre hafif (<40 µmol/L), orta (40-99 µmol/L) ve şiddetli (≥100 µmol/L) olarak gruplandırıldı. GİHK'nın şiddeti ve UDKA tedavisine verilen olumlu veya olumsuz yanıtın perinatal sonuçlar üzerine etkisi araştırıldı.

Bulgular: GİHK tanısı koyulan toplamda 200 gebe çalışmaya dahil edildi. Hastaların %65 (n=130)'inde hafif GİHK%21 (n=42)'sinde orta şiddetli GİHK ve %14 (n=28)'inde şiddetli GİHK saptandı. GİHK tanısıyla takip edilen hastaların 4 (%2.0)'ünde ölü doğum gerçekleşti. Şiddetli GİHK hastalarında spontan preterm doğum oranı, orta ve hafif GİHK hastalarına kıyasla anlamlı olarak daha yüksekti (p<0.001). Şiddetli GİHK hastalarında ve UDKA tedavisine yanıt vermeyen hastalarda, ortalama doğum haftası, ortalama doğum ağırlığı, 1. ve 5. dakika Apgar skorları daha düşük, amniyon maisinde mekonyum varlığı, yenidoğan yoğun bakım ünitesi ihtiyacı ve ölü doğum oranları daha yüksekti.

Sonuç: GİHK ile komplike olan gebelikler fetal ve neonatal olumsuz sonuçlar açısından artmış riske sahiptir. Maternal serum SA düzeyleri hastalığın siddeti ve olumsuz perinatal sonuçlarla ilişkilidir. Bununla birlikte, UDKA tedavisine verilen klinik cevap, fetal ve neonatal sonuçları öngörmede etkili olabilir.

Anahtar kelimeler: Gebeliğin intrahepatik kolestazı, gebelik kolestazı, kolestaz, yenidoğan sonuçları, ursodeoksikolik asit.

ABSTRACT

Aim: To investigate the effects of serum bile acid (BA) levels and response to ursodeoxycholic acid (UDCA) treatment on perinatal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP).

Materials and Method: In this retrospective study, pregnancies followed for ICP at a tertiary center between January 2013 and January 2018 were analyzed. ICP severity was classified according to serum BA levels as mild (<40 µmol/L), moderate (40-99 µmol/L) and severe (≥100 µmol/L). The effects of the severity of ICP and the positive or negative response to UDCA treatment on perinatal outcomes were investigated.

Results: A total of 200 pregnant women diagnosed with ICP were included in the study. Mild ICP was detected in 65% (n=130) of the patients, moderate ICP in 21% (n=42) and severe ICP in 15% (n=28). Stillbirth occurred in 4 (2.0%) of the patients. Spontaneous preterm birth rate was significantly higher in patients with severe ICP compared with patients with moderate and mild ICP (p<0.001). Mean gestational age, mean birth weight, 1st and 5th minute Apgar scores were lower, and the presence of meconium in the amniotic fluid, need for neonatal intensive care unit and stillbirth rates were higher in patients with severe ICP and patients who did not respond to UDCA treatment.

Conclusion: Pregnancies complicated by ICP have an increased risk for adverse fetal and neonatal outcomes. Maternal serum BA levels are associated with disease severity and adverse perinatal outcomes. The clinical response to UDCA treatment may be effective in predicting fetal and neonatal outcomes.

Key words: Cholestasis, cholestasis of pregnancy, intrahepatic cholestasis of pregnancy, neonatal outcomes, ursodeoxycholic acid.

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GİRİŞ

Gebeliğin intrahepatik kolestazı (GİHK), gebelikte ortaya çıkan karaciğer hastalıkları arasında viral hepatitten sonra en yaygın görülen hastalıktır (1). GİHK insidansı toplumlar arasında değişkenlik göstermektedir. Avrupa ülkelerinde ve Asya'da %1-2 oranında görülürken Kuzey Amerika'da %0.1 oranında görüldüğü rapor edilmiştir (2). GİHK'nın etiyolojisi tam olarak bilinmemekle birlikte, genetik altyapısı GİHK'na müsait olan gebelerde, gebelikte artan östrojen ve progesteron düzeylerinin ve çevresel faktörlerin hastalığın patogenezinde rol oynadığı düşünülmektedir (3,4). Temelde gebelikte artan östrojene bağlı değişiklikler ile birlikte safra asitlerinin (SA) atılamamasına bağlı olarak artmış serum SA düzeyleri görülür. GİHK genellikle 3. trimesterde başlayan, el ve ayak tabanlarında olan ve geceleri şiddetlenen kaşıntı ile kendini gösterir. Şikayetler doğumdan sonra birkaç gün içinde azalır ve 2 hafta içinde tamamen kaybolur (5). Hastaların büyük çoğunluğunda karaciğer fonksiyon testlerinde (KCFT) artış mevcuttur. Tanıda en önemli biyokimyasal belirteç safra asitlerinin (SA) plazma düzeyidir ve sağlıklı gebelere göre 10 ila 100 kat artmıştır. Aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP) ve 5'nukleotidaz seviyeleri de artabilir (6).

GİHK'da genellikle maternal prognoz iyidir ve gebelik sonrası bulgular geriler. Öte yandan, fetal prognoz çok değişkendir ve preterm eylem, amniyotik sıvıda mekonyum varlığı, fetal distress ve fetal ölümle ilişkili olduğu düşünülmektedir (7,8,9). Fetal komplikasyonların patofizyolojisi net olmamakla birlikte yüksek serum SA düzeylerinin kardiyomyozitler üzerine etki ederek aritmilere sebep olduğu düşünülmektedir (10). Ayrıca yüksek serum SA düzeylerinin plasental vasküler yatakta vazokonstruksüyona neden olarak fetal distress, asfiksi, fetal ölümlere ve oksitosin reseptörleri üzerine etki ederek de spontan preterm eyleme sebep olduğu gösterilmiştir (11,12). Tedavide asıl amaç maternal ve fetal sonuçları iyileştirmektir ve bu amaçla günümüze kadar birçok ajan kullanılmıştır. Ancak günümüzde en etkili olduğu düşünülen ajan ursodeoksikolik asittir (UDKA). UDKA'nın hem karaciğer üzerinde hem de maternal-plasental safra asiti transportu üzerine etkileri olduğu gösterilmiştir (13-17).

GİHK ile komplike olan gebeliklerde maternal ve fetal komplikasyonlar göz önünde bulundurulduğunda, gebelik sonuçlarını iyileştirmek için takip, tedavi protokolu ve hastaların doğum zamanının planlanması büyük önem taşımaktadır. Bu çalışmanın amacı, GİHK ile komplike olan gebeliklerde serum SA düzeylerinin ve UDKA tedavisine verilen klinik cevabın perinatal sonuçlara etkisini araştırmaktır.

GEREÇ-YÖNTEM

Bu retrospektif çalışmada Ocak 2013 ile Ocak 2018 tarihleri arasında Sağlık Bilimleri Üniversitesi Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi'nde GİHK nedeniyle takip edilen gebelikler analiz edildi. Hastanemiz etik kurulu çalışmayı onayladı. (Onay tarihi/sayısı:09.01.2019/6). GİHK, açlık maternal serum SA yüksekliği (>10 µmol/L) ve/veya başka herhangi bir karaciğer hastalığı yokluğunda yüksek serum AST (>40 IU/L) ve ALT (>35 IU/L) seviyeleri ile birlikte olan progresif kaşıntı olarak tanımlandı. Kronik karaciğer hastalığı olan, kronik cilt hastalıkları olan, kolelitiazisi olan, karaciğeri etkileyen viral enfeksiyonu olan, alkol bağımlılığı veya sigara kullanımı olan, herhangi bir kronik ilaç kullanımı olan ve fetal anomali tespit edilen gebeler çalışma dışı bırakıldı.

Hastaların demografik özellikleri, GİHK tanı haftaları, tanı anındaki serum SA ve AST/ALT düzeyleri, tedavi alan hastalarda UDKA dozları, tedavi sonrası SA ve AST/ALT düzeyleri, spontan preterm eylem olup olmaması, yenidoğanların doğum haftaları, doğum kiloları, 1. ve 5. dakika Apgar skorları, amniyon maisinde mekonyum varlığı ve yenidoğan yoğun bakım ünitesi (YDYBÜ) ihtiyacı kaydedildi. GİHK şiddeti, serum SA seviyelerine göre hafif (<40 µmol/L), orta (40-99 µmol/L) ve şiddetli (≥100 µmol/L) olarak gruplandırıldı (18) ve gruplar arasında perinatal sonuçlar karşılaştırıldı. Maternal veya fetal diğer doğum nedenleri olmadığında, şiddetli GİHK olan gebelerde 35-36 gebelik haftasında, orta ve hafif şiddetli GİHK olan gebelerde 38-39 gebelik haftalarında elektif doğum gerçekleştirildi (19). Fetal gelişim kısıtlılığı (FGK), fetus karın çevresinin veya tahmini fetal ağırlığın 3 persentilin altında olması veya karın çevresi veya tahmini fetal ağırlık 3 ila 10 persentil arasında olan fetuslarda anormal Doppler akım bulgularının (umblikal arter pulsatilite inteksi >95 persantil, uterin arter pulsatilite inteksi >95 persantil ve serebroplasental oran <5 persantil) olması olarak tanımlandı (20). Gestasyonel diabetes mellitus (GDM), ilk defa gebelikte tespit edilen ve 75 gr oral glukoz tolerans testinde (OGTT) bir veya daha fazla değerin eşik değerlerin (açlık kan şekeri 92 mg/dl, birinci saat kan şekeri 180 mg/dl ve ikinci saat kan şekeri 153 mg/dl) üzerinde olması veya 100 gr OGTT'de iki veya daha fazla değerin eşik değerlerin (açlık kan şekeri 95 mg/dl, birinci saat kan şekeri 180 mg/dl, ikinci saat kan şekeri 155 mg/dl ve üçüncü saat kan şekeri 140 mg/dl) üzerinde olması olarak tanımlandı (21,22)

GİHK nedeniyle UDKA tedavisi alan gebeler, tedavi sonrası serum SA ve AST/ALT değerlerindeki düşüş ve başlangıç şikayetlerinin gerilemesi göz önüne alınarak tedaviden fayda gören ve görmeyen olarak iki gruba ayrıldı. UDKA tedavisinin başlanmasından sonraki iki hafta içerisinde kaşıntı şikayetleri gerileyen ve karaciğer fonksiyon testleri normal seviyelere (SA <10 µmol/L ve/veya AST <40 IU/L ve ALT <35 IU/L) inen hastalar tedaviye yanıtlı olarak değerlendirildi. UDKA tedavisine verilen olumlu veya olumsuz yanıtın perinatal sonuçlar üzerine etkisi araştırıldı.

İstatistiksel analiz

Araştırma verilerinin istatistiksel analizi SPSS for Windows 11 paket programı kullanılarak yapılmıştır. Analizlerde tanımlayıcı istatistikler yüzde (%), ortalama ± standart sapma olarak ifade edilmiştir. Kategorik değişkenlerin istatistiksel anlamlılığını belirlemek için Pearson Ki-kare testi veya Fisher testi kullanıldı. Değişkenlerin normal dağılıma uygunluğu Kolmogrov Smirnov testi ile incelenmiştir. İki sürekli değişkenin karşılaştırılmasında, normal dağılıma uyan sürekli değişkenler için Student t testi; normal dağılıma uymayan sürekli değişkenler için Mann Whitney U testi kullanılmıştır. İkiden fazla sürekli değişkenin karşılaştırılmasında normal dağılıma uyan sürekli değişkenler için ANOVA Varyans Analizi; normal dağılıma uymayan sürekli değişkenler için Kruskal Wallis Varyans Analizi kullanılmıştır. İstatistiksel anlamlılık için p değeri <0.05 olan durumlar anlamlı olarak kabul edilmiştir.

BULGULAR

GİHK tanısı koyulan toplamda 200 gebe çalışmaya dahil edildi. Hastaların %65 (n=130)'inde hafif GİHK, %21 (n=42)'sinde orta şiddetli GİHK ve %14 (n=28)'inde şiddetli GİHK vardı. Hastaların GİHK şiddetine göre ayrılmış gruplarda ortalama yaşları, önceki gebelik öyküleri, mevcut gebelikteki komplikasyonların (FGK, GDM ve spontan preterm eylem) Tablo-1'de gösterilmiştir.

Tablo 1. Gebeliğin intrahepatik kolestazının şiddetine göre ayrılmış gruplarda ortalama yaş, önceki gebelik öyküsü ve gebelikte eşlik eden komplikasyonlar

Değişkenler		Hafif (n=130)	Orta (n=42)	Şiddetli (n=28)	p değeri
Yaş (yıl)		29.1 ± 5.6	29.3 ± 5.4	28.3 ± 5.1	0.611
Parite	**0**	75 (57.7)	22 (52.4)	13 (46.4)	0.329
	1	35 (26.9)	12 (28.6)	9 (32.1)	
	≥2	20 (15.4)	8 (19.0)	6 (21.4)	
GİHK öyküsü		21(16.2)	4 (9.5)	13 (46.4)	**0.001**
Ölü doğum öyküsü		5 (3.8)	1 (2.4)	6 (21.4)	**0.002**
Fetal gelişim kısıtlılığı		12 (9.2)	5 (11.9)	3 (10.7)	0.639
GDM		36 (27.6)	12 (28.6)	6 (21.4)	0.789
Spontan preterm eylem		22 (16.9)	10 (23.8)	15 (53.6)	**0.001**

Değerler ortalama ± standart sapma, sayı ve yüzde (%) olarak belirtilmiştir.

Kısaltmalar: GDM, gestasyonel diyabetes mellitus; GİHK, gebeliğin intrahepatik kolestazı.

Şiddetli GİHK olan gebelerde ölü doğum öyküsü ve GİHK öyküsü daha yüksekti (sırasıyla, p=0.002 ve p<0.001). Spontan preterm eylem oranları şiddetli GİHK hastalarında orta ve hafif GİHK hastalarına kıyasla anlamlı olarak daha yüksekti (p<0.001). GİHK şiddetine göre ayrılmış gruplarda tanı haftaları, UDKA tedavi dozu, tedavi sonrası şikayetlerde gerileme, tanıdaki ve tedavi sonrasındaki serum SA, AST ve ALT değerleri Tablo-2'de gösterilmiştir.

Tablo 2. Gebeliğin intrahepatik kolestazının şiddetine göre ayrılmış gruplarda tanı haftaları, UDKA tedavi dozu, tedavi sonrası şikayetlerde gerileme, tanıdaki ve tedavi sonrasındaki serum SA, AST ve ALT değerleri

Değişkenler		Hafif (n=130)	Orta (n=42)	Şiddetli (n=28)	p değeri
Tanıdaki gebelik yaşı (hafta)		34.1 ± 4.2	33.1 ± 4.1	30.4 ± 6.3	**0.001**
Tanıdaki KCFT	**SA (µmol/L)**	20.2 ± 7.6	48.6 ± 11.9	116.1 ± 52.4	**0.001**
	AST (IU/L)	83.2 ± 83.0	137.5 ± 161.4	149.4 ± 145.2	**0.002**
	ALT (IU/L)	137.5 ± 147.1	204.6 ± 249.2	217.4 ± 174.1	**0.004**
UDKA tedavi dozu (mg/kg)		11.4 ± 3.1	11.7 ± 3.6	13.2 ± 3.5	0.091
Tedavi sonrası KCFT	**SA (µmol/L)**	13.4 ± 9.1	24.4 ± 18.3	66.2 ± 37.2	**0.001**
	AST (IU/L)	90.1 ± 146.2	98.1 ± 119.3	98.7 ± 84.1	0.198
	ALT (IU/L)	53.5 ± 77.5	59.6 ± 57.9	64.1 ± 53.4	0.113
Semptomlarda gerileme		54 (79.4)	15 (62.5)	7 (41.1)	**0.001**

Değerler ortalama ± standart sapma, sayı ve yüzde (%) olarak belirtilmiştir.

Kısaltmalar: AST, aspartat aminotransferaz; ALT, alanin aminotransferaz; KCFT, karaciğer fonksiyon testleri; SA, safra asiti; UDKA, ursodeoksikolikasit.

Şiddetli GİHK hastalarının ortalama tanı haftası hafif GİHK hastalarına kıyasla daha düşüktü (p<0.001). Ortalama UDKA tedavi dozu şiddetli GİHK hastalarında daha yüksek olsa da gruplar arasında anlamlı fark yoktu (p=0.091). Şiddetli GİHK hastalarının tedavi sonrasında serum SA düzeyleri hala daha yüksek iken, AST ve ALT düzeylerinde anlamlı fark yoktu (sırasıyla, p<0.001, p=0.198 ve p=0.113). Hafif GİHK hastalarının %52.3 (n=68)'nde, orta GİHK hastalarının %57.1 (n=24)'inde ve şiddetli GİHK hastalarının %60.7 (n=17)'sinde tanı sırasında kaşıntı şikayeti vardı. Hastaların tedavi sonrası kaşıntı şikayetlerindeki gerileme karşılaştırıldığında, hafif ve orta GİHK hastalarında şikayetlerin gerileme oranı şiddetli GİHK hastalarına kıyasla daha yüksekti (p<0.001).

GİHK şiddetine göre ayrılmış gruplarda yenidoğan sonuçları Tablo-3'te gösterilmiştir.

Tablo 3. Gebeliğin intrahepatik kolestazı şiddetine göre ayrılmış gruplarda yenidoğan sonuçları

Değişkenler	Hafif (n=130)	Orta (n=42)	Şiddetli (n=28)	p değeri
Doğum haftası	36.3 (31 - 41)	36.2 (30 - 39)	34.0 (27 - 37)	**0.001**
Doğum ağırlığı (gr)	2926 ± 590	2754 ± 584	2276 ± 605	**0.001**
1. dk Apgar skoru	7.5 ± 1.0	7.2 ± 1.1	6.2 ± 2.3	**0.002**
5. dk Apgar skoru	8.9 ± 0.8	8.6 ± 0.7	7.8 ± 2.3	**0.001**
Fetal disstres	9 (6.9)	6 (14.3)	6 (20.0)	0.061
Mekonyum varlığı	10 (7.7)	7 (16.7)	18 (64.3)	**0.001**
YDYBÜ ihtiyacı	31 (23.8)	19 (45.2)	24 (85.7)	**0.001**
Ölü doğum	0 (0.0)	1 (2.4)	3 (10.7)	**0.003**

Değerler ortalama ± standart sapma, minimum – maksimum, sayı ve yüzde (%) olarak belirtilmiştir.

Kısaltmalar: YDYBÜ, yenidoğan yoğun bakım ünitesi.

Şiddetli GİHK hastalarında ortalama doğum haftası, ortalama doğum ağırlığı, 1. ve 5. dakika Apgar skorları daha düşüktü. Benzer şekilde, şiddetli GİHK hastalarında amniyon maisinde mekonyum varlığı, YDYBÜ ihtiyacı ve ölü doğum oranları daha yüksekti. GİHK tanısıyla takip edilen toplamda 200 hastadan 4 (%2.0)'ünde ölü doğum gerçekleşti. Ölü doğum yapan hastalar arasında saptanan en düşük serum SA düzeyi 49 µmol/L, en yüksek serum SA düzeyi 170 µmol/L'ydi. Fetal distress şiddetli GİHK hastalarında daha yüksek oranda görülmesine rağmen gruplar arasında anlamlı fark yoktu (p=0.061). Hastaların %29.5 (n=59)'ünde UDKA tedavisine yanıt varken, %25.0 (n=50)"nde UDKA tedavisine yeterli yanıt yoktu. Hastaların %45.5 (n=91)'inde tedavi yanıtı beklenmeden doğum gerçekleştirildi. UDKA tedavisinden fayda gören ve görmeyen hastaların tanı haftaları, tanıdaki serum SA, AST ve ALT düzeyleri ve yenidoğan sonuçları Tablo-4'te gösterilmiştir.

Tablo 4. UDKA tedavisinden fayda gören ve görmeyen hastaların tanı haftaları, tanıdaki serum SA, AST ve ALT düzeyleri ve yenidoğan sonuçları

Değişkenler		Tedaviye yanıt		p değeri
	Yok (n=50)	Var (n=59)		
Tanıdaki gebelik yaşı (hafta)		30.2 ± 3.1	31.3 ± 4.2	0.682
Tanıdaki KCFT	**SA (µmol/L)**	42.2 ± 40.8	35.1 ± 33.7	0.796
	AST (IU/L)	100.6 ± 97.6	95.3 ± 85.9	0.961
	ALT (IU/L)	164.9 ± 155.0	158.3 ± 179.1	0.612
Doğum haftası		35.2 ± 2.1	37.2 ± 2.1	**0.001**
Doğum ağırlığı (gr)		2539 ± 673	3102 ± 515	**0.019**
1. dk Apgar skoru		6.6 ± 1.4	7.6 ± 0.7	**0.001**
5. dk Apgar skoru		8.3 ± 0.8	8.9 ± 0.5	**0.001**
Fetal disstres		11 (22.0)	2 (3.4)	**0.001**
Mekonyum varlığı		16 (32.0)	5 (8.5)	**0.001**
YDYBÜ ihtiyacı		30 (60.0)	13 (22.0)	**0.001**
Ölü doğum		1 (2.0)	1 (1.7)	0.540

Değerler ortalama ± standart sapma, sayı ve yüzde (%) olarak belirtilmiştir.

Kısaltmalar: AST, aspartat aminotransferaz; ALT, alanin aminotransferaz; KCFT, karaciğer fonksiyon testleri; SA, safra asiti; UDKA, ursodeoksikolikasit; YDYBÜ, yenidoğan yoğun bakım ünitesi.

Tedaviden fayda gören ve fayda görmeyen hastaların tanıdaki gebelik yaşları, serum SA, AST ve ALT düzeyleri arasında anlamlı fark yoktu (sırasıyla, p=0.682, p=0.796, p=0.961 ve p=0.612). UDKA tedavisinden fayda gören hastalarda yenidoğan ortalama doğum haftası, doğum ağırlığı, 1. ve 5. Dakika Apgar skorları daha yüksekti ve bu yenidoğanlarda fetal disstres oranı, amniyon maisinde mekonyum varlığı ve YDYBÜ ihtiyacı daha düşüktü.

TARTIŞMA

Bu çalışma GİHK ile komplike olan gebeliklerde maternal serum SA düzeylerinin ve UDKA tedavisine verilen klinik cevabın fetal ve neonatal prognoz üzerine olan etkilerinin kapsamlı bir değerlendirmesini sunmaktadır. Çalışmamızda, şiddetli GİHK gelişen gebeliklerde spontan preterm doğum daha yaygındı. Genel popülasyonda FGK prevalansının %10 ve GDM prevalansının %7.8 olduğu göz önünde bulundurulduğunda çalışmamızda GİHK gelişen gebeliklerde FGK oranı genel popülasyonla benzerken GDM oranı genel popülasyona göre daha yüksekti (23,24). Öte yandan, FGK ve GDM sıklığı ile hastalık şiddeti arasında ise anlamlı bir ilişki bulunamadı. Fetal distress, şiddetli GİHK hastalarında daha yüksek oranda görülmesine rağmen gruplar arasında anlamlı fark yoktu. Neonatal sonuçlar değerlendirildiğinde, yenidoğanların doğum ağırlıkları, 1. ve 5. dakika Apgar skorları şiddetli GİHK hastalarında daha düşük izlendi. Şiddetli GİHK ile komplike olan gebeliklerde yenidoğanlarda mekonyum varlığı, YDYBÜ ihtiyacı ve ölü doğum oranları daha yüksekti. Bu bulgular GİHK şiddeti ile olumsuz perinatal sonuçlar arasında ilişki olduğunu ve GİHK ile komplike olan gebeliklerde hastalığın şiddetine göre gebelik takibi protokollerinin belirlenmesi gerektiğini göstermektedir.

Bu çalışmada ikinci olarak UDKA tedavisine verilen olumlu veya olumsuz yanıtın perinatal sonuçlar üzerine etkisi araştırıldı. Sonuçlarımız, tanı anındaki gebelik yaşının ve serum SA, AST ve ALT düzeylerinin UDKA tedavisine olumlu yanıtı öngörmede değerli belirteçler olmadığını ve serum SA, AST ve ALT değerlerinin yüksek veya düşük olmasının tedaviye yanıtı etkilemediğini göstermektedir. Şiddetli GİHK hastalarında UDKA tedavi dozu orta ve hafif GİHK hastalarına göre daha yüksek olsa da aradaki fark anlamlı değildi. Bu bulgular UDKA tedavisine başlarken hastalığın şiddetine göre doz ayarlamanın tedaviye yanıtı etkilemeyebileceğini düşündürdü. UDKA tedavisine olumlu yanıt veren hastalarda yenidoğanların doğum haftaları, doğum ağırlıkları, 1. ve 5. dakika Apgar skorları daha yüksek, fetal disstres, amniyon maisinde mekonyum varlığı, YDYBÜ ihtiyacı daha düşüktü. Bu bulgular UDKA tedavisiyle semptomları gerileyen ve serum SA, AST ve ALT değerleri düşen hastalarda daha olumlu neonatal sonuçlar beklenebileceğini gösterdi.

Pata ve ark.'nın yaptığı bir çalışmada toplamda 3710 gebe arasında 32 hasta kolestaz tanısı almış ve bu hastaların sonuçları değerlendirilmiştir. Multipar olguların %16,6'sında daha önceki gebelikte kolestaz öyküsü olduğu, %21,8'inde ise aile öyküsünün olduğu saptanmıştır (25). Bizim çalışmamızda, şiddetli GİHK gelişen gebelerin %43.3'ünde daha önceki gebeliklerinde GİHK öyküsü mevcuttu. Bu bulgu, önceki gebelikte GİHK öyküsünün olmasının mevcut gebelikte şiddetli GİHK gelişmesi açısından bir risk faktörü olabileceğini düşündürdü. Benzer şekilde, şiddetli GİHK gelişen gebeliklerde önceki gebeliklerde ölü doğum öyküsü daha yüksekti. Bu bulgu, ölü doğumla sonuçlanan önceki gebeliklerde tanı koyulamamış bir şiddetli GİHK olabileceğini düşündürmektedir. Sonuçlarımız, önceki gebeliğinde şiddetli GİHK veya ölü doğum öyküsü olan gebelerin mevcut gebeliğinde kötü perinatal sonuçların önlenmesi için daha yakından takip edilmesi gerektiğini ortaya koymaktadır.

Şiddetli GİHK gelişen gebeliklerde spontan prematür doğum oranının daha yüksek olması bu gebeliklerde yüksek serum SA düzeylerinin oksitosin reseptörlerini aktive ederek doğum eylemini başlatmasıyla açıklanabilir. Brouwers ve ark.'nın yaptığı 210 GİHK olgusunu içeren bir çalışmada, şiddetli GİHK hastalarında hafif GİHK grubuna göre tanı ve doğum haftalarının çok daha düşük olduğu gösterilmiştir (26). Bu çalışmada şiddetli GİHK olgularında spontan preterm eylem oranı %19 olarak bulunmasına karşın bizim çalışmamızda spontan preterm eylem oranı şiddetli GİHK olgularında %53.6 bulunmuş olup çok daha yüksekti. Yenidoğan sonuçları değerlendirildiğinde serum SA düzeylerinin kötü perinatal sonuçlarla yüksek düzeyde ilişkisinin olduğu düşünülmektedir. Ancak, şiddetli GİHK olgularında spontan preterm eylemin çok daha sık görülmesi sebebiyle hastaların doğum haftalarının, doğum kilolarının ve Apgar skorlarının düşük olması ve YDYBÜ ihtiyaçlarının fazla olması beklenen bir durumdur. Dolayısıyla, şiddetli GİHK hastalarında daha kötü neonatal sonuçların serum SA düzeylerindeki yükseklikten mi yoksa şiddetli GİHK gelişen hastaların daha yüksek oranda preterm doğum yapmasından mı kaynaklandığını net olarak söyleyememekteyiz.

GİHK tedavisinde plaseboya karşı UDKA'nın etkinliğini araştıran ve 605 GİHK olgusunu içeren randomize kontrollü bir çalışmada, UDKA tedavisinin maternal kaşıntı skoru ve serum ALT düzeylerinde iyileşme sağlarken, ortalama serum SA düzeylerinde bir iyileşme olmadığı bildirildi (27). Bununla birlikte, bu çalışmada, perinatal ölüm, erken doğum ve YDYBÜ ihtiyacı gibi olumsuz fetal ve neonatal sonuçlar plaseboya kıyasla UDKA tedavisi alan hastalarda benzerdi. Bu çalışmaya benzer şekilde, plasebo ile UDKA tedavisinin etkinliğini araştıran bir meta-analizin sonuçları UDKA tedavisinin temel fetal ve neonatal sonuçlarda net bir iyileşme sağlamadığını gösterdi (28). Öte yandan, bu meta-analizin sınırlaması, hastaların ne kadarının ilacı düzenli olarak aldığının ve faydalı bir etki elde etmek için bir eşik ilaç dozu ve tedavi süresinin gerekli olup olmadığının net olmamasıdır. Bizim çalışmamızda, UDKA tedavisine yanıt veren hastalarda yenidoğan sonuçları daha iyiydi. Bununla birlikte, UDKA tedavisine yanıt alınan hastalarda, yenidoğanların doğum haftaları ve doğum kiloları daha yüksek olduğundan, yenidoğan sonuçlarındaki bu iyileşmenin UDKA tedavisinin direkt bir etkisi olup olmadığı net değildir.

Çalışmamızın bazı kısıtlılıkları vardı. Birincisi, çalışmanın retrospektif tasarımından kaynaklanan doğal kısıtlılıklardır. İkincisi ise, hem GİHK şiddetine göre ayrılmış gruplarda hem de UDKA tedavisine yanıta göre ayrılmış gruplarda gebelik yaşı eşleştirilmiş kontrol gruplarının olmamasıdır. Bu durum hem şiddetli GİHK hastalarında hem de UDKA tedavisine yanıt alınamayan hastalarda yenidoğan sonuçlarının prematüriteye mi bağlı olduğu yoksa hastalığın şiddetine mi bağlı olduğunu net olarak değerlendirmemizi engelledi. Öte yandan, mevcut çalışmanın standart takip ve tedavi protokollerinin uygulandığı üçüncü basamak tek bir merkezde yürütülmesi ve nispeten yüksek sayıda hasta içermesi bu çalışmanın güçlü yönleridir.

SONUÇ

GİHK ile komplike olan gebelikler fetal ve neonatal olumsuz sonuçlar açısından artmış riske sahiptir. Maternal serum SA düzeyleri hastalığın siddeti ve olumsuz perinatal sonuçlarla ilişkilidir ve şiddetli GİHK olan hastalarda bu riskler en yüksek düzeydedir. Bununla birlikte, serum SA düzeylerinin yanı sıra UDKA tedavisine verilen klinik cevap da fetal ve neonatal sonuçları öngörmede etkili olabilir. Bu sebeple, GİHK ile komplike olan hastalar sadece serum SA düzeylerine göre değil, aynı zamanda hastaların tedaviye verdikleri cevaba göre de değerlendirilmelidir. Hastaların takiplerinde bu iki parametrenin beraber kullanılması ve uygun takip ve tedavi protokollerinin oluşturulması perinatal sonuçları iyileştirebilir.

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Özgün Araştırma / Original Article

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Evaluation of the myeloperoxidase/paraoxonase1 ratio as the determinant of dysfunctional HDL in polycystic ovary syndrome

Polikistik over sendromunda disfonksiyonel HDL'nin göstergesi olarak miyeloperoksidaz/paraoksonaz1 oranının değerlendirilmesi

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ÖZ

Amaç: Miyeloperoksidaz/paraoksonaz1(MPO/PON1) oranının, oksidatif stresin bir ölçüsü olan disfonksiyonel HDL(d-HDL)'yi yansıttığı bilinmektedir. Bu çalışmada, polikistik over sendromunda (PKOS) MPO/PON1 oranının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif çalışmaya toplam 123 kadın dahil edildi. PKOS tanılı kadınları içeren çalışma grubu (n=63), sağlıklı kadınların bulunduğu kontrol grubu (n=60) ile karşılaştırıldı. Grupların sosyodemografik özellikleri ve klinik özellikleri kaydedildi. Serum HDL düzeyi, MPO ve PON1 aktiviteleri değerlendirildi.

Bulgular: PKOS hastalarında MPO aktivitesinde artış ve PON1 aktivitesinde azalma gözlendi (sırasıyla; p<0,0001 ve p=0,007). Sağlıklı kontrollere kıyasla PKOS hastalarında d-HDL anlamlı olarak yüksek bulundu (0,50 (0,12) vs. 0,56 (0,24), p<0,0001). Oksidatif parametreler ile PKOS ilişkili bulgular arasında da anlamlı ilişkiler gözlendi (p<0.05).

Sonuç: Çalışmamızda, d-HDL olarak tanımlanan artmış MPO/PON1 oranının yanı sıra artmış MPO ve azalmış PON1 aktiviteleri de PKOS hastalarında artmış oksidatif stresi desteklemektedir. Sonuçlarımız, yaşamının erken dönemlerinde bile PKOS hastalarında oksidatif stres ve dislipidemiye işaret etmesi yönünden dikkat çeker niteliktedir.

Anahtar Kelimeler: Disfonksiyonel HDL; MPO/PON1; Oksidatif stres; PCOS.

ABSTRACT

Aim: The myeloperoxidase/paraoxonase1(MPO/PON1) ratio is known to reflect the dysfunctional HDL(d-HDL) which is a measure of oxidative stress.This study aimed to evaluate the MPO/PON1 ratio in polycystic ovary syndrome(PCOS).

Materials and Method: This prospective study included a total of 123 patients. The study group including the women with the diagnosis of PCOS (n=63) was compared to the control group including the healthy women (n=60). Sociodemographic characteristics,and clinical features of the groups were recorded. Serum HDL level, MPO, and PON1 activities were evaluated.

Results: The PCOS patients were observed to have increased MPO and decreased PON1 activities (p<0.0001 and p=0.007, respectively). The d-HDL and was found to be significantly higher in PCOS patients compared to the healthy controls (0.56 (0.24) vs. 0.50 (0.12), p<0.0001). There were also significant associations between the oxidative parameters and PCOS related findings (p<0.05).

Conclusion: Besides the increased MPO/PON1 ratio which defined as d-HDL, the increased MPO and decreased PON1 activities also supported the increased oxidative status in PCOS patients. Our results may be considered to draw attention to oxidative stress and dyslipidemia in PCOS patients, even in the early periods of the women life.

Keywords: Dysfunctional HDL; MPO/PON1; Oxidative stress; PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most commonly seen endocrine and metabolic disorder among the women at reproductive age, with the incidence of 15% (1). The PCOS was also indicted for increased risk of chronic inflammation of arterial walls, atherosclerosis, and coronary artery diseases. It has been associated with long-term health problems including dyslipidemia, increased oxidative stress, chronic inflammation, and metabolic syndrome. Even the etiopathogenesis of the PCOS has not been fully understood yet, the dysfunctional lipoprotein particles are reported to associate with increased oxidative distress and pro-inflammatory state in PCOS patients (2, 3).

High-density lipoprotein (HDL) is an atheroprotective molecule mediating reverse cholesterol transport. It has antioxidant, anti-inflammatory, antithrombotic, and antiapoptotic activity through a number of antioxidant enzymes including paraoxonase 1 (PON1). The PON1 is known to integrate into the structure of HDL and contribute for stabilization of HDL to exert the HDL mediated antioxidant features (4-6). On the other hand, HDL constitutes a heterogeneous group of subclasses. The discrepancy in the size and function of the HDL particles result in a contrary impact which leads to HDL to contribute for oxidative stress and inflammatory processes (7, 8). The MPO is an oxidant enzyme taking role in immune defence. The MPO was shown to lead modification of HDL molecules and impair its normal functioning (8, 9). The PON1 and MPO were reported to associate with the structural and functional distortion of the HDL particles (10).

The HDL isolated from patients with high MPO/PON1 ratio exhibited attenuated anti-inflammatory properties and impairment of cholesterol efflux capacity. In literature, the ratio of MPO/PON1 was defined as dysfunctional HDL (d-HDL) which reflects the proinflammatory and oxidizing HDL subclasses in various diseases with an underlying oxidative status (6, 11, 12). The oxidative status is one of the underlying mechanisms which was reported to take role in PCOS etiopathogenesis. There are also evidences for the alteration in functioning, size and number of HDL particles in PCOS (4, 13). On the other hand, the MPO/PON1 ratio has not yet been evaluated in PCOS patients. In this study, we aimed to evaluate the women with PCOS in terms of MPO/PON1 ratio, which is known to reflect the d-HDL subclasses.

MATERIALS AND METHODS

This prospective case-control study was conducted at Ankara City Hospital, Department of Obstetrics and Gynecology, between the November 2022 – May 2023 . The study protocol was approved by the Hospital's Ethics Committee (#E1-20-1188) and the study was carried out through the rules of the Helsinki Decleration. Written informed consent was obtained from all the participants prior to the enrollment.

All the participants were included from the women who consequently applied to the outpatient clinics. Study group included the women with the diagnosis of PCOS (n=63). Control group included the healthy women with regular menstrual periods, who applied for contraceptive counseling (n=60).

The uterine fibroids, endometriosis, history of pelvic surgery, ongoing pregnancy and/or breastfeeding, thyroid dysfunctions including Hashimoto thyroiditis and Grave's disease, hepatic dysfunctions, renal insufficiency, hypertension, cardiovascular diseases, type 1 or type 2 diabetes mellitus, obesity, smoking, infectious conditions, primary adrenal insufficiency, neurologic diseases, psychiatric disorders, autoimmune syndromes and diseases, the history of malignancy and exposure to chemotherapeutics or radiotherapy were defined as exclusion criteria.

Antecubital vein blood sampling was performed from all participants after 12 hours fasting. The complete blood count, liver and renal functioning tests, and serum HDL level were analyzed. The MPO and PON1 were anlyzed from the centrifuged serum samples which were stored at - 80°C until the whole samples were collected.

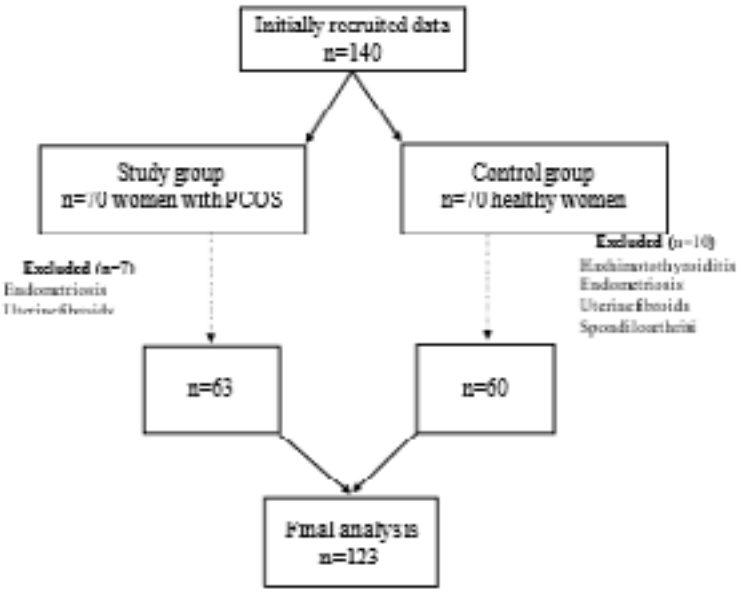
For measuring PON1 activity, we measured the rate of paraoxon hydrolysis by monitoring the absorbance at 412 nm. Molar absorptivity coefficient at 8.5 pH, which was 18290 M−1 cm−1 was used to calculate the amount of generated p-nitrophenol. PON1 activity was defined as U/L serum. Measurement of myeloperoxidase activity was performed by using Human Myeloperoxidase ELISA kit (Elabscience Biotechnology Co. Ltd., Wuhan, China) (Cat.No.:E-BC-K074-M), which detects the range of 19.42-893.31 U/L.

The SPSS V22.0 (Armonk, NY: IBM Corp., USA) was used in statistical analysis. Independent samples t-test was used for normally distributed continuous data (mean ± standard deviation). The Mann-Whitney U test was used for not normally distributed continuous variables [median (interquartile range)]. In a 95% confidence interval, a P-value <0.05 is considered statistically significant. Spearman's correlation analysis was applied to determine statistical dependence of variables. The G-Power V3 (Heinrich-Heine-Universität, Düsseldorf, Germany) was used to calculate sample size. The posthoc power analysis was also performed. This study achieved a 89 % power with a 0.5 effect size and a 0.05 error rate, considering the comparison of PON1 activity between the independent two groups including n=63 PCOS patients and n=60 healthy controls.

RESULTS

A total of 140 women were evaluated at the start of the study. The women who detected to have any of the exclusion criteria were also excluded through the study course. Final analysis included 123 participants. The flow diagram of the study is presented as fig 1.

Fig 1. The flow diagram of the study.



The demographic data, clinical findings and the analyses regarding oxidative markers are presented in table 1.

Table 1. Demographic data, clinical findings and laboratory parameters of the participants.

Variables	PCOS (n=63)	Control (n=60)	*P*-value
Age *years* Mean ± SD	27.60 ± 4.90	26.91 ± 4.38	0.675
HDL *mg/dl* Median (IQR)	44 (7)	57 (9)	0.001*
BMI *kg/m²* Median (IQR)	24.35 (8)	22.32 (5)	0.005*
MPO *U/L* Median (IQR)	94.38 (11.09)	91.70 (3.54)	<0.0001*
PON1 *U/L* Mean ± SD	163.19 ± 29.83	181.03 ± 32.53	0.007*
d-HDL *MPO/PON1* Median (IQR)	0.56 (0.24)	0.50 (0.12)	<0.0001*

**P*-value <0.05 is considered as statistically significant.

PCOS: Polycystic ovary syndrome; BMI: Body mass index; MPO: Myeloperaoxidase activity;
PON 1: Paraxonase 1 activity; HDL: High density lipoprotein; d-HDL: Dysfunctional HDL;
N/A: Non-applicable.

The correlations of the oxidative parameters and PCOS related findings are demonstrated in table 2.

Table 2. Correlations between the oxidative markers and PCOS related parameters.

		d-HDL	**HDL**	**PON1**	**MPO**	**BMI**
BMI	r	0.285	-0.204	-0.086	0.387	N/A
	P-value	0.005	0.058	0.407	<0.001	N/A
MPO	r	0.632	0.143	0.042	N/A	
	P-value	<0.0001	0.349	0.645	N/A	
PON1	r	-0.843	-0.067	N/A		
	P-value	<0.0001	0.563	N/A		
HDL	r	-0.117	N/A			
	P-value	0.296	N/A			
d-HDL	r	N/A				
	P-value	N/A				

P-value <0.05 is considered as statistically significant.

PCOS: Polycystic ovary syndrome; BMI: Body mass index; MPO: Myeloperaoxidase activity;
PON 1: Paraxonase 1 activity; HDL: High density lipoprotein; d-HDL: Dysfunctional HDL;
N/A: Non-applicable.

DISCUSSION

Previous studies suggested that oxidative stress, dyslipidemia, and chronic low-grade subclinical inflammation are mainly responsible for the complex endocrine and metabolic conditions in PCOS. Changes in the lipoprotein composition have been shown to associate with the distorted functioning of HDL and increased oxidative status (4, 14). In this study, increased MPO and decreased PON1 activities were observed in PCOS patients. The d-HDL and was found to be significantly higher in PCOS patients compared to the healthy controls.

In literature, PCOS has been reported to associate with decreased antioxidant capability and prominent inflammatory state (4, 15). Previous studies showed quantitative alterations in LDL and HDL levels, in women with PCOS (2, 3, 16). In line with the previous reports, our results also revealed significantly low levels of serum HDL in PCOS patients. However, the previous reports on HDL functioning were through directly analyzing the structural nd functional characteristics of the HDL particles. To the best of our knowledge, this study is the first one to evaluate the MPO/PON1 ratio as the indicator of d-HDL in PCOS patients. Independent from the quantitative changes, Phelan et al. reported that the qualitative changes in lipoprotein fractions may lead to oxidized lipoprotein formations which were more atherogenic and inflammatory subfractions. These subfractions were suggested to associate with the increased oxidative stress in PCOS patients (16). McPherson et al. also indicated the d-HDL as an altered subclass of HDL which may promote the oxidation of LDL particles (17). Zhang et al. reported the impairment in antioxidant properties of HDL in PCOS my contribute to PCOS etiopathogenesis (14). Pazderska et al. implied the possible associations of HDL dysfunction and changes in the size of LDL molecules with the undesired metabolic consequences of the PCOS by increasing the oxidative load (18). Considering the previous researches, the low levels of HDL and high d-HDL in PCOS group in this study appears to be attributable to the altered oxidative status. On the other hand, the correlation between the serum HLD levels and d-HDL was not significant. In this regard, our present findings may be interpreted as the changes in HDL level and d-HDL may regard the quantitative and qualitative aspect of oxidative stress, respectively, in PCOS patients.

The HDL molecule is known to have antioxidant, anti-inflammatory and antiatherogenic activities. In a study of Van Lenten et al., the HDL was reported to become proinflammatory under oxidative stress, which impedes the protective effect of HDL against LDL mediated oxidation (19). Baskol et al. showed that the oxidative stress and inflammatory conditions associate with the decrease in PON1 activity (15). PON 1 is a circulating esterase and lactonase which prevents the oxidation of lipids and also destroys the oxidized lipid formations. The PON1 achieves its antioxidant activity by interacting with apo A1 on HDL particles (3, 4). Different pathological conditions may lead dysfunctional HDL maturation and the shift of PON1 from the smaller HDL particles having more potent antioxidative activity to the larger HDL particles. The alteration in posttranslational modification of apo AI is also a prominent factor which may lead to HDL dysfunction and has been reported to be associated with reduced PON1 activity and decreased anti-inflammatory activity of HDL (17, 20). In a proteomic study conducted by Davidson et al., HDL 3 activities of different subjects were analyzed and PON1 levels were reported to directly correlate with the antioxidant activity of HDL (21). Perovic-Blagojevic et al. analyzed the association of oxidative status with HDL and LDL particle sizes, subclasses, and PON1 activity distribution on HDL subclasses in women with PCOS. They showed a significant association between the oxidative stress and pro-atherogenic changes in lipoprotein subclass profiles in PCOS patients (4). In this study, we observed significantly decreased PON1 activity in PCOS patients, besides the significant increase in d-HDL. The PON1 did not significantly correlate with the HDL level, despite its strong negative correlation with d-HDL. Our results may be support the literature which revealed the decreased PON1 activity to lead impairment in antioxidant characteristics of the HDL.

The MPO is an enzyme which take role in killing of microorganisms by neutrophils, monocytes, and macrophages. However, the release of MPO and its reactive byproducts at inflammatory sites can damage adjacent tissues and cells, thus contributing to the pathogenesis of diseases. The importance of locally formed highly reactive MPO derived oxidants was accounted to the selective and direct binding of MPO to apoAI (8). Daugherty et al. revealed that high levels of MPO in atheromas had the key role to impair the functionality of HDL particles to provide the reverse transport of the cholesterol (9). MPO was also shown to promote the modification of apo AI on HDL particles. Zheng et al. reported that in vitro modification of apoAI on HDL particles by MPO was observed to lead to loss of cholesterol acceptor activity of apoAI (22). Panzenboeck et al. showed that MPO-modified HDL was more susceptible to degradation by macrophages, which reverses the lipid-accepting capability of HDL to a lipid-loading molecule (23). The MPO was also reported to have possible role in increased oxidative status and endothelial damage in PCOS patients and was reported to associate with the obesity. Ribeiro et al. revealed increased MPO activity which was also related with the insuline resistance in PCOS patients, even through at a young age period (24). Victor et al. reported increased rate of ROS and MPO concentrations in PCOS patients which may underly the clinical complications of PCOS (25). In line with the previous reports, the current study revealed increased MPO activity and d-HDL in PCOS patients. MPO was also directly correlated with the BMI. Thus, our results appears to be in line with the literature which indicated the MPO activity to take role in PCOS etiopathogenesis through the oxidative mechanisms and dyslipidemia.

The qualitative and quantitative alterations in LDL and HDL levels were reported to significantly associate with the BMI in women with PCOS (4, 16). Obesity was also reported to favor the subclass redistribution towards the HDL smaller particles, which has lower antioxidant capacity (4). In this study, the obese subjects were excluded. However, the BMI of PCOS group was significantly higher than healthy controls. The BMI of the PCOS patients was also observed to have a tendency towards the overweight. Gambineri et al. reported that the low level of HDL may lead high prevalence of metabolic syndrome in PCOS (26). In this study, the HDL level did not exhibit significant correlation with BMI, even the predictive value was close to the significance level. On the other hand, the direct correlation between the d-HDL and the BMI was remarkable to indicate the possible significance of the functional alterations of HDL in term of the metabolic state.

The prospective design of the study provided some advantages

which enabled us to cope with some confounders. Since the obesity is known to be associated with increased oxidative status in PCOS, we defined the obesity as an exclusion criterion. However this study has some shorcomings which should be mentioned. The younger age period may alleviate the impact of oxidative stress and the age range of our participants was placed in a young age period. Even the serum HDL level was lower than the control group, the decrement may not be interpreted as very deep. In this aspect, the associations between the d-HDL and long term effects of PCOS including the atherosclerotic changes could not be evaluated in this cohort. The studies evaluating the clinical associations between the d-HDL and PCOS through a wider age range may provide further contribution to the literature.

CONCLUSION

In this study, the MPO/PON1 ratio as the indicator of d-HDL was significantly higher in PCOS patients compared to the healthy controls. Besides the increased MPO/PON1 ratio, the increased MPO and decreased PON1 activities observed in PCOS patients also supported the increased oxidative status. Our results may be considered to draw attention to oxidative stress and dyslipidemia in PCOS patients, even in the early periods of the women life.

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Analysis of the Gynecologic Cancer Surgery with Pre-pandemic Protocols in a COVID-19 Free Cancer Center

COVID-19 Hasta İçermeyen Bir Kanser Merkezinde Pandemi Öncesi Protokollerle inekolojik Kanser Cerrahisinin Analizi

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ABSTRACT

Objective: COVID-19 has caused a rapid transformation in the healthcare system, including in particular, the care of vulnerable cancer patients. The aim of this study was to present our clinical experience in gynecological cancer surgeries in a COVID-19-free cancer hospital during the pandemic.

Materials and Methods: A retrospective analysis was made of the data of patients with ovarian, endometrium, cervix and vulva cancers who were treated with surgery between March 2020 and March 2021, with particular focus on the complication rates on day 30, and at the end of one year.

Results: The study included a total of 74 patients with mean age of 59 years. The most common diagnosis was ovarian cancer (48.6%) followed by endometrial (43.2%), cervical (6.8%) and vulvar cancer (1.4%). Most of the patients were in advanced stage (FIGO 3 and 4) of ovarian (86%), endometrial (59.4%) and cervical local advanced (60%) cancer. The complication rate was 17.6 %. Surgery was delayed in one patient with a preoperative positive polymerase chain reaction (PCR) test for COVID-19 infection, and none of the patients had a positive test result in the early postoperative period.

Conclusion: COVID-19-free institutions for cancer surgery, is an effective treatment strategy in the context of the pandemic. The results of this study indicate that continuity of cancer treatment can be achieved safely, with strict adherence to COVID-19 precautions for both patients and healthcare workers.

Keywords: COVID-19, gynecological cancer, surgery, treatment

ÖZ

Amaç: COVID-19, özellikle savunmasız kanser hastalarının bakımı dahil olmak üzere sağlık sisteminde hızlı bir dönüşüme neden olmuştur. Bu çalışmanın amacı, pandemi döneminde COVID-19'dan arınmış bir kanser hastanesinde jinekolojik kanser ameliyatlarındaki klinik deneyimimizi sunmaktı.

Gereç ve Yöntemler: Mart 2020-Mart 2021 tarihleri arasında cerrahi tedavi uygulanan over, endometrium, serviks ve vulva kanserli hastaların verilerinin özellikle 30. gün ve 1. günün sonundaki komplikasyon oranlarına odaklanılarak retrospektif analizi yapıldı.

Bulgular: Çalışmaya yaş ortalaması 59 olan toplam 74 hasta dahil edildi. En sık tanı yumurtalık kanseri (%48,6) idi, bunu endometrial (%43,2), servikal (%6,8) ve vulvar kanser (%1,4) izledi. Hastaların çoğu ileri evrede (FIGO 3 ve 4) over (%86), endometrial (%59,4) ve serviks lokal ileri (%60) kanseriydi. Komplikasyon oranı %17.6 idi. Ameliyat öncesi COVID-19 enfeksiyonu için polimeraz zincir reaksiyonu (PCR) testi pozitif olan bir hastada ameliyat ertelendi ve ameliyat sonrası erken dönemde hastaların hiçbirinde pozitif test sonucu çıkmadı.

Sonuç: Kanser cerrahisi için COVID-19'dan arınmış kurumlar, pandemi bağlamında etkili bir tedavi stratejisidir. Bu çalışmanın sonuçları, hem hastalar hem de sağlık çalışanları için COVID-19 önlemlerine sıkı bir şekilde uyulması ile kanser tedavisinin sürekliliğinin güvenli bir şekilde sağlanabileceğini göstermektedir.

Anahtar Kelimeler: COVID-19, jinekolojik kanser, cerrahi, tedavi

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INTRODUCTION

The COVID-19 pandemic has had an unprecedented impact on healthcare worldwide causing enormous strain on healthcare services globally (1,2,3). Cancer patients are the most vulnerable patient group because of their urgent need for complex treatment and their suppressed immune system.

In the field of gynecological oncology, COVID-19 affects patient health directly with increased risk of infection and indirectly by decreasing hospital capacity for cancer treatment (4,5). All major societies, including gynecological oncology associations, made new recommendations for treatment protocols focusing on: 'less surgery, fewer hospital visits and more protective measures against the spread of COVID-19' (6,7). In this context, planned gynecological cancer surgeries were postponed or cancelled in many hospitals and medical centers, as they could not provide optimal conditions for patients and staff (8).

In this new environment, our hospital, which is a comprehensive cancer centre, was defined as a COVID -19-free hospital and was established as a reference centre for other institutions regarding priority oncological surgeries by the regional healthcare authorities. In these COVID-19-free hospitals, no COVID-19-positive patients were hospitalized and only cancer patients with a negative test result were allowed to have inpatient care. One visitor with a negative test result was permitted, and stayed in isolation in the hospital. Thus cancer surgeries have continued in our hospital since the beginning of the pandemic, with maximum attention paid to the medical safety of both patients and employees.

The primary outcome of this study was to evaluate the results, complications and reliability of gynecological cancer surgery performed during the pandemic period compared with the established complication rate of gynecological cancer surgery. The secondary endpoint was to evaluate the safety of the COVID-19-free cancer hospital policy on the surgical management of gynecological cancers during the pandemic.

MATERIALS AND METHODS

Approval for the study was granted by the Ethics Committee of the Institutional Review Board of Local Hospitals, and the Ministry of Health Scientific Research Platform. Our center was declared a COVID -19-free hospital in the pandemic and focused only on cancer treatment. It became a reference center for regional hospitals and medical centers regarding priority oncological surgeries by the healthcare authorities.

The data of the patients who were operated on with the diagnosis of gynecological cancer at our center between March 2020 and March 2021 were retrospectively examined from a scan of the patient files. Patients with a diagnosis of gynecological cancer (ovarian cancer, cervical cancer, endometrial cancer, ovarian borderline tumor and vulvar cancer) for whom surgery was performed during the study period were included. Exclusion criteria were defined as patients with other types of gynecological cancer, such as breast cancer or trophoblastic tumor, and patients that did not have a surgical treatment plan for management of their cancer.

A gynecology oncologist evaluated all the patients. Radiological examinations such as ultrasound, magnetic resonance imaging, or computed tomography (CT) scans were requested if needed. All patients were required to have a preoperative routine blood analysis and a chest X-ray. Neoadjuvant chemotherapy was planned only for ovarian cancers according to Leuven selection criteria (9).

In the early stages of the pandemic, a COVID-19 PCR test and / or thorax CT were requested for patients with clinically suspected COVID-19 or a history of close contact with a confirmed case in the preoperative period. The COVID-19 PCR test was routinely applied 48 hours before the operation, according to the guidelines published by the health authorities in December 2020. There was no routine test for asymptomatic healthcare workers. According to the decision of the infectious diseases committee of the hospital, surgery for COVID-19-positive patients was delayed for one month and performed after a negative test result. The first vaccinations for COVID-19 were performed in January 2021 and began with healthcare personnel. None of the patients were vaccinated during the study period. Only the healthcare workers of the hospital were vaccinated. For asymptomatic patients, routine COVID-19 testing was not applied after the surgery.

Clinical records, laboratory and imaging findings of the patients were obtained from the hospital patient records. Demographic characteristics of the patients, comorbidities, type of surgery performed, histopathological features of the tumor, stage of the disease, early and late complications, duration of hospitalization, adjuvant therapy and COVID-19 status were recorded. Complications were evaluated according to the Clavien Dindo criteria (10).

Basic descriptive statistics were used to describe the results. Data were stated as frequency and percentage and mean±standard deviation (SD) values as appropriate. Statistical analyses were performed using SPSS vn. 22.0 software (Statistical Program for the Social Sciences).

RESULTS

The study included a total of 74 patients with a mean age of 58 years (range, 16–85 years). Patients were referred with ovarian (36/74, 48.6%), endometrial (32/74, 43.2%), cervical (5/74, 6.8%), or vulvar cancer (1/74, 1.4%). The clinicopathological characteristics of patients who underwent surgery are listed in Table 1.

Table 1. Baseline characteristics

Age(years) (median(range))	59 (16-85)
Age <65 years (n (%))	47 (63.51)
Age ≥65 years (n (%))	27 (36.49)
Comorbidity (n(%))	
Hypertension	42 (56.7)
Extragynecological malignancy history	3 (4.1)
Diabetes	27 (36.4)
History of respiratory disease	5 (6,7)
Without disease	21 (28.4)
Disease type (n(%))	
Over cancer (n(%))	36 (48.6)
Endometrium cancer (n(%))	32 (43.2)
Cervical cancer (n(%))	5 (6.8)
Vulvar cancer (n(%))	1 (1.4)

The most commonly performed procedures were total abdominal hysterectomy together with bilateral salphingoopherectomy, bilateral pelvic and paraaortic lymph node dissection and omentectomy. The surgical operations are presented in Table 2.

Table 2. Surgical Treatment

		n	%
TAH+BSO+BPPLND+Omentectomy	Endometrium /Ovarian cancer	61	82%
USO+BPPLND+ Omentectomy	Ovarian cancer	2	3%
Secondary / Terttiary Cytoreduction	Recurrent ovarian cancer	2	3%
TAH+BSO+Omentectomy +Appendectomy +Hemicolectomy+Peritonectomy	Ovarian cancer	3	4%
Hemivulvectomy	Vulvar cancer	1	1%
Wertheim +BPPLND	Cervical cancer	5	7%

TAH (Total Abdominal Hysterectomy, USO (Unilateral Salphingooopherectomy), BSO (Bilateral Salphingooopherectomy), BPLND (Bilateral Pelvic, Paraaortic Lymph Node Dissection)

A total of nine ovarian and endometrium cancer patients received neoadjuvant chemotherapy and 57 patients received adjuvant chemotherapy. The adjuvant and neoadjuvant therapies are shown in Table 3.

Table 3. Neoadjuvant / Adjuvant Treatment

	n	%
Adjuvant treatment		
Endometrium cancer	23	72%
Over cancer	30	83%
Cervical Cancer	4	80%
Neoadjuvant treatment		
Endometrium cancer	1	3%
Over cancer	8	22%

The COVID-19 PCR test was routinely applied 48 hours before the operation in the second half of the study period due to increased availability of the test, according to the guidelines published by the health authorities in June 2021.The surgery of one patient with a positive preoperative COVID-19 PCR test result was postponed for one month. After one month and 2 negative tests performed 24 hours apart, the surgery was performed. Neither the COVID-19 symptoms nor the COVID-19 test were positive in this patient in the perioperative and postoperative period.

Postoperative complications were seen in 13 patients (13/74, 17.6%), of which 5 were Clavien–Dindo grade 1 or 2 (7/13, 53.8%), and 7 (6/13 46.2%) were grade 3 or 4 (Table 4).

Table 4. Complications

Complication	ClavienDindo Grade	n	%
Superficial infection	I	4	5.4%
Urinary infection	II	2	2.7%
Deep infection	III	3	4 %
Hypercalcemia	II	1	1.3%
Transient ischemic attack	IIIa	1	1.3%
Anastomotic leakage	IIIb	1	1.3%
Acute renal failure	IVa	1	1.3%

Total number

The grade 3 and 4 complications occurred in patients with advanced stage cancers who underwent extensive surgery. The length of hospital stay was mean12 days (range, 6-51 days). In one patient who was re-operated on for anastomotic leakage, the length of hospital stay was 51 days, of which 14 days were in the intensive care unit. The surgical data of the patients are shown in Table 2.

None of the patients tested positive for COVID-19 with a PCR test in the early postoperative period (14 days), after discharge. There were five positive PCR tests for COVID-19 in the late period within two months.

DISCUSSION

In this study the setting of COVID-19-free institutions for the continuity of cancer surgery was evaluated from the perspective of complication rates and disease spread. Many hospitals had to delay surgical treatments during the pandemic (4,9,12). However, surgical cancer care poses genuine problems, because delayed diagnosis and treatment could worsen oncological outcomes (13,14). The COVID-19 outbreak had an impact on gynecological cancer surgeons, such as avoiding surgery in favor of radiotherapy or chemotherapy (15,16,17). In an Italian nationwide survey considering surgical decisions, it was seen that avoiding lymphadenectomy or sentinel lymph node mapping had occurred during this period (4).

Given its characteristics and focus on the treatment of cancer patients, the COVID-19-free cancer centers were designed to continue cancer care without a change in the treatment plan compared with the pre-COVID era. At the start of the study period, COVID-19 PCR testing was not systematically performed because of the low availability of tests at that time, as in many centers (18). However, it was routine in the second half of the study period. COVID-19 infection was detected in only one patient in that period, causing a delay of surgery for one month. None of the patients were diagnosed with COVID-19 during the early follow-up period of two weeks after discharge. However, there were eight positive PCR tests within two months after surgery indicating the importance of personal isolation and protection during the vulnerable period of cancer treatment. The low cancellation rate (1 out of 74 patients) and absence of COVID-19 during the early postoperative period indicates the success of the COVID-19-free cancer center policy from the perspective of disease control. Five patients were tested positive between 15 days and 2 months after surgery. In the early postoperative period, maximum care was taken in the hospital and at home in repect of disease spread. After that period, additional therapies, the need for follow-up visits, and decreased attention to personal protection could have influenced the risk of transmission and subsequent infection.

Major surgery is the principal treatment modality especially in ovarian cancer, which has the highest mortality rate within this group (18,19). Most of the affected women were diagnosed at an advanced stage because early stage disease is usually asymptomatic and symptoms of late-stage disease are non-specific. Advanced stage diseases require more extensive surgery and frequent adujuvant treatment. Surgical treatment and adjuvant modalities, such as chemotherapy and radiotherapy cause immune suppression, which may affect complication rates (20). Pandemics may potentially further delay the diagnosis because of accessibility to outpatient screening.

De Santiago et al. reported the results of 126 patients treated in a partial COVID-19-free hospital and reported an 11% complication rate (18). That study included 60% breast cancer patients and less than 5% of the series were advanced stage ovarian cancer. The Society of Gynecological Oncology has suggested use of the Elective Surgery Acuity Scale (ESAS) for planning and most cases of gynecological cancer fall into tier 3a/b, for which the recommended action is not to delay surgery (7). As seen from the current study results, 74 gynecological cancer surgeries were safely managed during the pandemic, including advanced stage patients and complicated surgeries, avoiding delays or cancellations. The complication rate of 17.6% may seem to be excessive but most of the patients in this series were advanced stage (FIGO Stage 3 and 4) ovarian (86%); endometrial (59.4%) and cervical (60%) cancer. The vast majority of the Clavien–Dindo grade 3 and 4 complications were secondary to major surgery such as hemicolectomy and Wertheim in patients with advanced stage ovarian and cervical cancer (10). Three intrabdominal infections were conservatively treated with parenteral antibiotic treatment. A previous multicenter study including nearly 3000 major gynecological oncology operations reported a 30% complication rate within this group, with the highest complication rate observed in ovarian cancer patients (21). The current study showed that the postsurgical complications were similar both in percentage and clinical prognosis when compared with several centers in the pre-COVID-19 period.

During pandemics, small discrepancies within the many steps of cancer care beginning from admission, postoperative follow-up, to complex surgical operations and intensive care may adversely affect the overall outcome and risk of infection (22,23). The current study, conducted in a COVID-19-free hospital, demonstrated that gynecological cancer surgery, can be performed safely without changing the treatment approach. A COVID-19-free path in referral hospitals for cancer treatment helped both cancer patients and healthcare workers to achieve similar outcomes compared with the pre-COVID era. As surgeries gradually increase again in the post-pandemic period, it should be a priority to use hospital resources in a fair and responsible manner for cancer patients.

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The Effect of The Number of Preovulatory Follicles Developed by Ovulation Induction with GND and Clomiphene Citrate for IUI Treatment in Unexplained Infertility on Pregnancy Rates

Açıklanamayan İnfertilitede IUI Tedavisinde GND ve Klomifen Sitrat İle Ovulasyon İndüksiyonu İle Gelişen Preovulatuar Folikül Sayısının Gebelik Oranlarına Etkisi

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ÖZ

Amaç: Bu çalışmanın amacı açıklanamayan infertilitesi olan çiftlerde over stimülasyonlu (OS) aşılamada oluşan dominant folikül sayısının gebelik sonuçlarını etkileyip etkilemediğini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza 24-39 yaşları arasında açıklanamayan infertilitesi olan ve OS ile IUI uygulanan 217 çift katılmıştır. Hastalar klinik olarak gebe olanlar ve olmayanlar olmak üzere 2 gruba ayrılarak yaş, monofollikül ve bifolikül gelişimi, infertilite süresi, tedavi başlama günü, hcg günü, önde gelen folikül çapı, endometrium kalınlığı, dominant folikül sayısı ve tedavi tipi açısından karşılaştırıldı.

Bulgular: Açıklanamayan infertilite nedeni ile IUI yapılan 217 hastada klinik gebelik olan ve olmayan gruplar arasında dominant folikül sayısı açısından anlamlı fark bulunmadı (p=0,73). Endometriyal kalınlık ile tedavi başarısı arasında pozitif ancak düşük bir korelasyon vardı (Spearman's korelasyon katsayısı değeri = 0,14, p=0,03). Alıcı çalışma karakteristik eğrisi analizi, gebelik başarısını öngörmek için endometriyal kalınlık için optimal kesme değerinin 9,5 mm (%55,0 duyarlılık, %65,0 özgüllük) olduğunu ortaya koydu.

Sonuç: Sonuç olarak açıklanamayan infertilitede klinik gebelik oranları açısından gonadotropinlerin oral ajanlara üstünlüğü olmadığı, bu nedenle tedaviye daha az invaziv ve daha az maliyetli oral ajanlarla başlanması gerektiği kanaatindeyiz. Ayrıca over stimülasyonu ile oluşturulan dominant folikül (monofolikül veya bifolikül) sayısının klinik gebelik başarısını etkilemediğini, ancak endometriyal kalınlığın gebelik oranları ile yakından ilişkili olduğunu ve dikkat edilmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: monofolikül, bifolikül, açıklanamayan infertilite, endometrial kalınlık, intrauterin inseminasyon

ABSTRACT

Aim: The aim of this study is to investigate whether the number of dominant follicles formed in IUI with OS affects pregnancy outcomes in couples with unexplained infertility.

Material and Method: 217 couples aged 24-39 years with unexplained infertility and treated with IUI by way of ovarian stimulation participated in our study. The patients were divided into 2 groups of which the first included the clinically pregnant and the second did not, and were compared in terms of age, monofollicle and bifollicle development, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness, number of dominant follicles and treatment type.

Results: Of the 217 patients who underwent IUI for unexplained infertility, no significant difference was found between the groups with and without clinical pregnancy in terms of the number of dominant follicles (p=0.73). There was a positive but low correlation between endometrial thickness and treatment success (Spearman's correlation coefficient value = 0.14, p=0.03). The receiver operating characteristic curve analysis revealed that the optimal cut-off value for endometrial thickness to predict pregnancy success was 9.5 mm (55.0% sensitivity, 65.0% specificity).

Conclusions: As a result, we suggest that gonadotropins are not superior to oral agents in terms of clinical pregnancy rates in unexplained infertility, therefore treatment should commence with less invasive and less costly oral agents. Furthermore, we think that the number of dominant follicles (monofollicles or bifollicles) created by ovarian stimulation does not affect clinical pregnancy success, but endometrial thickness is closely related to pregnancy rates and deserves attention.

Keywords: monofollicle, bifollicle, endometrial thickness, intrauterine insemination, unexplained infertility

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INTRODUCTION

Unexplained infertility accounts for 10-30% of infertile couples and is diagnosed by determining tubal patency and with the normal ovulation function and semen analysis (1). Treatment is usually empirical as no underlying cause can be identified. However, the chance of spontaneous pregnancy is high in untreated couples (2). IUI, by way of ovarian stimulation (OS) with the use of oral agents or gonadotropins, plays an important role in the treatment. Additionally, IUI and IVF are also among the treatment options within a natural cycle.

The aim of the treatment other than to achieve live birth is also to minimize the risk of multiple pregnancy and OHSS (3). There are views suggesting the use of less invasive and more cost-effective treatments when dealing with cases of unexplained infertility (2). However, studies show that although IUI treatment with gonadotropins increases the risk of OHSS and multiple pregnancy, the rates of live births are also higher (1). Therefore, in order to reduce the risk of multiple pregnancy, there are strict cancellation practices when dealing with the formation of more than two follicles, such as cancelling the treatment cycle and imposing a coitus ban (4).

Many studies have investigated factors that affect IUI outcomes in unexplained infertility. One study reported that a women's age, smoking status, and the number of treatment cycles has an affect on conception (5). Another study revealed that higher maternal and paternal ages adversely affected pregnancy and that IUI is an effective method in couples with unexplained infertility (6). In a randomized cohort of women with unexplained infertility, it was shown that biochemical and clinical androgen measurements did not predict the live birth rate after ovarian stimulation treatment (7). In unexplained infertility, the factors affecting the treatment and live birth rates are still controversial because the cause cannot be determined clearly. Many factors have been investigated. However, studies on whether the number of dominant follicles formed in IUI treatment by way of OS affect pregnancy rates are not common in the literature. In this respect, this study is different.

The aim of our study is to investigate whether the number of dominant follicles formed in IUI treatment by way of OS affect pregnancy outcomes in couples with unexplained infertility.

MATERIALS AND METHODS

217 couples aged 24-39 years who applied to the IUI unit of our hospital due to unexplained infertility between January 2021 and January 2022 and were treated with IUI participated in our study. Ethics committee approval was obtained from the ethics committee unit of the city hospital (21/1085). The unexplained infertility diagnosis was made by looking at the couples' semen analysis, hysteresalpingogram, transvaginal ultrasound, serum basal hormone values performed on the 2nd day of the cycle, and serum midluteal phase progesterone values. All of the spouses of the patients had normal spermiogram results based on at least two semen analyzes according to World Health Organization (WHO) 2010 criteria, which were confirmed by the same urologist. In all hysteresalpingograms, there were no abnormalities that could cause uterine and tubal factors. Ovarian, follicular and endometrial pathologies were not observed in transvaginal ultrasounds in any of the women. The serum basal hormones administered on the 2nd day of the cycle consisted of FSH, LH, E2, PRL, and TSH. Couples with PCOS, endometriosis, uterine or tubal factor infertility, decreased ovarian reserve, male factor infertility and those that smoked were excluded from the study. Also, patients with a body mass index >=30 kg/m2 and patients with additional systemic diseases were not included in the study. The patients' age, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness information, applied treatment procedures and pregnancy status were scanned from our hospital archive and recorded. Beginning from the 2nd or 3rd day of the cycle, patients received controlled ovarian stimulation with clomiphene citrate or 37.5-150 IU HMG. From the 6th day of the cycle, transvajinal ultrasound and regular monitoring of serum e2 levels were used to track follicular development. When at least one ≥16-18 mm follicle was seen in the transvaginal ultrasonography, a urinary hCG dose of 10,000 IU was administered.

The patients were divided into groups based on the number of preovulatory follicles developed, including those with 1 preovulatory follicle (monofollicular) and those with 2 preovulatory follicles (bifollicular), as well as those who underwent IUI with clomiphene citrate based medication and those who underwent IUI with gonadotropin based medication. All patients underwent intrauterine insemination 36 hours after hCG administration, and sexual intercourse was allowed after insemination. In addition, patients who received gonadotropin were given 200mg/day vaginal progesterone supplementation for luteal support following the transfer. Clinical pregnancy was defined as the presence of a gestational sac with fetal cardiac activity detected by ultrasound at least 4 weeks after insemination. Pregnant and non-pregnant patients were compared in terms of monofollicle and bifollicle formation, age, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness and treatment type (clomiphene citrate and GND).

Statistical analyses was performed using the Statistical Package for the Social Sciences (SPSS) ver. 21.0 (IBM Corp., Armonk) NY, US). The Kolmogorov-Smirnov test was used to determine the normality of the data. Descriptive parameters were expressed as the medians (interquartile range) for continuous variables and as numbers and percentages for categorical variables. Chi-square test was used to analyze the data and compare the groups (i.e., pregnant vs. non-pregnant). Degrees of association between the achieving pregnancy and endometrial thickness were calculated using Spearman's rank correlation coefficient. Receiver operating characteristic curves were used to determine the cut-off values of the endometrial thickness for achieving pregnancy. A $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 217 women fulfilled the inclusion criteria and enrolled in the study. The clinical characteristics for all patients according to the groups are summarized in Table 1.

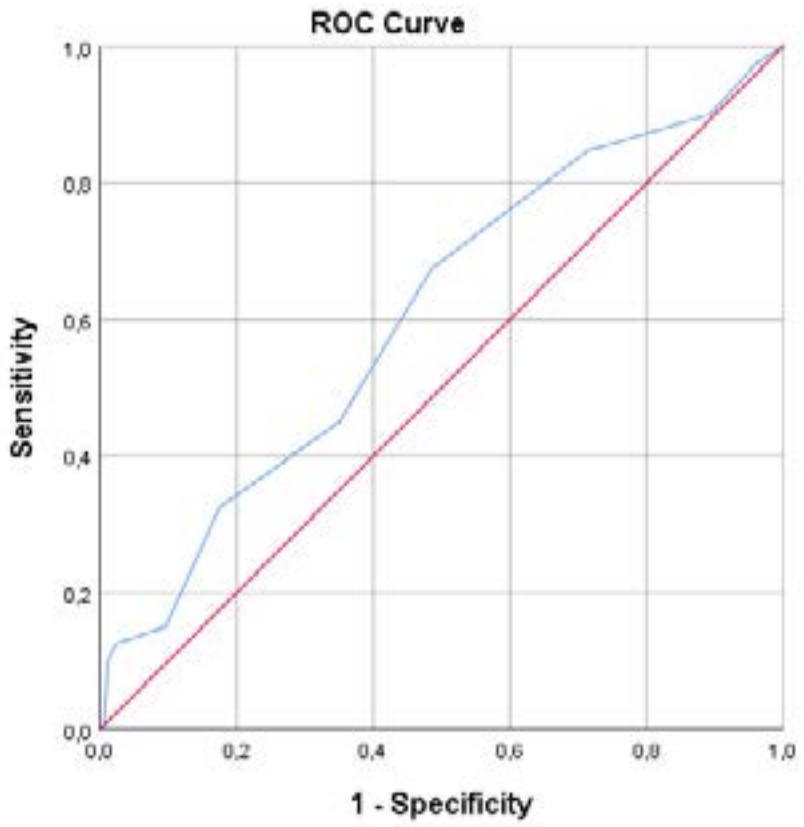
Table 1: Characteristics of patients, overall and according to treatment success.

Characteristic	*All patients (n=217, %100)*	*Pregnant (n=40, %18.4)*	*Non-pregnant (n=177, %81.6)*	*p value*
Age (years)	28.0±8.0	26.0±8.8	28.0±8.0	0.70
Infertility period (years)	3.0±2.0	3.0±1.0	3.0± 2.0	0.13
FSH value (U/L)	6.7±1.9	6.2± 1.3	6.8± 2.0	0.21
Estradiol value (ng/L)	38.0±19.0	35.5±18.7	38.0±18.5	0.77
Medication type (%) Gonadotropin Clomiphene citrate	 65.0 (30.0) 152.0 (70.0)	 13.0 (6.0) 27.0 (12.5)	 52.0 (24.0) 125.0 (57.5)	0.69
Treatment start day	3.0±1.0	3.0±1.0	3.0±2.0	0.79
hCG administration day	13.0±2.0	14.0±3.8	13.0±2.0	0.05
Leading Follicle Diameter (mm)	19.0±2.0	19.0±3.0	19.0±3.0	0.27
Dominants Follicle Count (%) One Two	 136.0 (62.7) 81.0 (37.3)	 26 (11.9) 14(6.5)	 110 (50.8) 67 (30.8)	0.73
Endometrial thickness (mm)	9.0±3.0	9.0±3.0	8.0±3.0	**0.03***

Data are expressed as median mean±standard deviation or number (%).

The groups were not different regarding clinical features except for endometrial thickness (p =0.03). Even though the relationship between endometrial thickness and treatment success (pregnancy) was positive, it was low (Spearman's correlation coefficient value = 0.14, p=0.03). The receiver operating characteristic curve analysis revealed that the optimal cutoff value of endometrial thickness for predicting the achievement of pregnancy was 9.5 mm (55.0% sensitivity, 65.0% specificity). (Fig.1)

Fig.1: Receiver operating characteristics curve of endometrial thickness for determining the treatment success (i.e., pregnant vs. non-pregnant) (area under the curve: 0.60, standard error: 0.05).



DISCUSSION

In our study, we investigated whether the number of dominant follicles formed in IUI treatment by way of OS affects pregnancy outcomes in couples with unexplained infertility. We did not detect a significant difference in the number of dominant follicles between the groups with and without clinical pregnancy (p=0.73). Similarly, we did not observe a statistically significant difference among age, duration of infertility, treatment initiation day, hCG day, leading follicle diameter, and treatment type (clomiphene citrate and GND). However, there was a positive but low correlation between endometrial thickness and treatment success (pregnancy), and we demonstrated that the optimal thickness was 9.5 mm.

In studies conducted in unexplained infertility, factors affecting pregnancy success have been investigated in various ways. In one study, it was reported that gonadotropins were more effective than oral agents in couples with unexplained infertility (1). The cohrane analysis of Cantineau et al. in 2021 demonstrated that gonadotropins increase the chance of live birth more than oral agents, but may also cause an increase in the risk of multiple pregnancy (8). Similarly, a meta-analysis conducted by Wessel et al. reported that gonadotropins were more successful than oral agents in unexplained infertility and the risk of multiple pregnancy could be disregarded (9). However, another study showed that women's age and smoking had a negative effect on pregnancy outcomes and stated that as the number of treatment cycles increased, the pregnancy rate also increased. BMI, treatment regimens, the type of infertility, endometrial thickness, and the timing of insemination did not have any significant prognostic value (5). Furthermore, a comprehensive study conducted by Huang et al. showed that IUI with oral agents was not significantly different from gonadotropin cycles, and IUI with oral agents was recommended due to the fact that it controlled the rate of multiple pregnancy in unexplained infertility (10). One study reported that, in unexplained infertility, the success of IUI increased as the duration of infertility shortened (11). Correspondingly, another study found that infertility duration and age were associated with pregnancy rates (12). In contrast, in our study, we demonstrated that infertility duration, treatment initiation day, hcg day, leading follicle diameter and treatment type (clomiphene citrate and GND) had no effect on clinical pregnancy outcomes. In these studies, IUI success was generally shown as a live birth. However, we defined the success of IUI as clinical pregnancy. This situation and the fact that our study is a retrospective study are the limitations of our article.

While several studies reported that there were no difference in pregnancy rates between IUI performed on the day of hCG and IUI performed 36 hours after hCG (13, 14), another study found that IUI performed after ovulation had higher pregnancy rates than IUI performed on the day of ovulation (15). Therefore, in order to increase the sucess rate of our study, we performed the IUI 36 hours after hCG administration. Moreover, a study on the leading follicle diameter on the hCG day suggested that lead follicle diameter associated with increased pregnancy rates was 19-20mm (16), while another study suggested that it was 21-22mm (17). However, we did not find a significant difference between leading follicle diameter and clinical pregnancy rates in our study.

There are contradictions about the effect of endometrial thickness on pregnancy success in IUI cycles in unexplained infertility. In a randomized controlled study conducted by Quaas et al., although it was thought that increased endometrial thickness was associated with high live birth rates, it was reported that there were significant live pregnancy rates even in thin endometrium and that the cycle should not be canceled due to thin endometrium (18). Nonetheless, another studystated that endometrial thickness was important for achieving viable pregnancy, and in patients with unexplained infertility, the optimal thickness for IUI treatment was considered to be 7.7 mm (19). A meta-analysis that was conducted revealed that there was no connection between endometrial thickness and pregnancy rates in IUI cycles (20). On the other hand, a study conducted by Danhof et al. stated that there is no evidence of a significant connection between endometrial thickness and ongoing pregnancy (21). In contrast, Li et al. demonstrated that clinical pregnancy rates improved as the endometrial thickness increased (22). In our study, we demonstrated that there is a positive but low correlation between endometrial thickness and treatment success (clinical pregnancy), and the optimal thickness is 9.5 mm. Moreover, a strong aspect of our study is that there are no studies investigating the impact of the number of dominant follicles (monofollicle or bifollicle) on clinical pregnancy rates in IUI treatment by way of OS for unexplained infertility. There is a recent study in the literature on this subject. Merviel et al. reported that the highest chance of pregnancy with IUI was during the first two cycles and with bifollicular response to stimulation in women with unexplained infertility (23).

In conclusion, we suggest that gonadotropins are not superior to oral agents in terms of clinical pregnancy rates in unexplained infertility, therefore we recommend that treatment should be initiated with less invasive and less costly oral agents. Furthermore, we think that the number of dominant follicles (monofollicle or bifollicle) created by ovarian stimulation does not affect the success of clinical pregnancy, however, we consider that endometrial thickness is significantly correlated with pregnancy rates and, thus, we believe it should be given careful consideration.

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Özgün Araştırma / Original Article

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Fetal malnütrisyonlu term bebeklerde ilk iki yaştaki büyüme, glukoz, insülin ve lipid profili

Growth, glucose, insulin and lipid profile in the first two years of term infants with fetal malnutrition

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ÖZ

Amaç: Fetal dönemde büyüme kısıtlılığı, ileri yaşlarda metabolik hastalıkların gelişimini etkileyebilir. Bu çalışmada, fetal malnütrisyonu olan ve olmayan term yenidoğan bebeklerin ilk iki yaştaki büyümelerinin ve ikinci yaştaki glukoz, insülin ve lipid profillerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya Mayıs 2019 ile Ekim 2019 tarihleri arasında hastanemizde doğan, CANSCORE yöntemi kullanılarak fetal malnütrisyon saptanan ve saptanmayan term bebekler alındı. Umblikal kord kanında insülin, glukoz, total kolesterol, düşük yoğunluklu lipoprotein (LDL), yüksek yoğunluklu lipoprotein (HDL), çok düşük yoğunluklu lipoprotein (VLDL) kolesterol, trigliserid değerlerine bakıldı. Bu bebeklerin iki yaşına kadar büyümeleri takip edildi. İkinci yıl sonunda aynı paramtrelere yeniden bakıldı.

Bulgular: Fetal malnutrisyon saptanan 40 bebekten 26'sı, fetal malnutrisyon saptanmayan 40 bebekten 22'si iki yıl boyunca takip edildi. Fetal malnütrisyonu olan bebeklerin 6. ayında vücut ağırlığı, boy uzunluğu ve baş çevresinin, fetal malnütrisyonlu olmayan bebeklere göre daha yüksek olduğu ancak 12 ve 24. ayda bu farkın gerilediği görüldü. Yaşamının ikinci yılında bakılan glikoz, insülin, total kolesterol, LDL kolesterol, HDL kolesterol düzeyleri arasında her iki grup arasında anlamlı farklılık yokken, VLDL kolesterol ve trigliserid düzeyleri fetal malnütrisyonu olan grupta anlamlı olarak daha yüksek saptandı.

Sonuç: Fetal malnütrisyonlu bebeklerde yaşamının ilk 6 ayındaki hızlı kilo artışı erken çocukluk dönemindeki lipid profilini etkileyebilir.

Anahtar Kelimeler: Fetal malnütrisyon, büyüme, kolesterol, trigliserid

ABSTRACT

Aim: Growth restriction in the fetal period may affect the development of metabolic diseases in later ages. In this study, it was aimed to compare the growth of the first two years of age and the glucose, insulin and lipid profiles in the second year of term newborn babies with and without fetal malnutrition.

Materials and Methods: Term infants born in our hospital between May 2019 and October 2019, with and without fetal malnutrition detected using the CANSCORE method were included in the study. Insulin, glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL) cholesterol, triglyceride values were measured in the umbilical cord blood. The growth of these babies was followed up to the age of two. At the end of the second year, the same parameters were looked at again.

Results: 26 out of 40 babies with fetal malnutrition and 22 out of 40 babies without fetal malnutrition were followed for two years. It was observed that body weight, height and head circumference of babies with fetal malnutrition were higher at 6 months compared to babies without fetal malnutrition, but this difference regressed at 12 and 24 months. While there was no significant difference between the two groups in terms of glucose, insulin, total cholesterol, LDL cholesterol, and HDL cholesterol levels in the second year of life, VLDL cholesterol and triglyceride levels were found to be significantly higher in the group with fetal malnutrition.

Conclusion: Rapid weight gain in the first 6 months of life in infants with fetal malnutrition may affect the lipid profile in early childhood.

Keywords: Fetal malnutrition, growth, cholesterol, triglyceride

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GİRİŞ

Fetal malnütrisyon (FM), klinik olarak cilt altı yağ dokusunun ve kas kitlesinin normal miktara ulaşamaması ya da belirgin intrauterin kaybı ile karakterizedir. Fetal beslenme probleminin en yaygın görülen şekli intrauterin büyüme kısıtlılığıdır (1). İntrauterin büyüme kısıtlılığı, FM ile ilişkildir. FM, intrauterin büyüme kısıtlılığına ilerleyebilir (2). İntrauterin dönemde fetal yağ dokusunun maturasyonu gebeliğin ikinci trimestrında başlar ve üçüncü trimestrında daha da olgunlaşır (3). Yağ dokusu, lipid ve daha da önemlisi glikoz metabolizması için gereklidir, yağ dokusu eksik olduğunda malnütrisyona, fazla olduğunda obeziteye neden olmaktadır (4). FM'de intrauterin dönemde besin eksikliği, endokrin sistemin programlanmasına yol açmakta ve fetal yaşamda enerji tasarrufu sağlamaktadır. Besin eksikliği doğumdan sonra da devam ederse tolere edilebilir; ancak doğumdan sonra aşırı beslenme olursa tolere edilemez ve aşırı enerjiye yol açar (5). Bu da yağ dokusunda aşırı birikime ve patolojik bir glikoz toleransına neden olur. Bu hipotez tutumlu fenotip hipotez olarak adlandırılır. İntrauterin büyüme kısıtlılığı olan bebeklerin postnatal dönemde hızlı büyümesi gelecekteki sağlık durumunun belirleyicisidir (6,7).

FM ve intrauterin büyüme kısıtlılığı, ileri yaşamda kardiovasküler hastalıklar, hiperlipidemi, diabetus mellitus, obesite, metabolik sendrom görülme sıklığını arttırmaktadır (8). FM'li bebeklerin postnatal dönemdeki beslenmesi, büyüme ve gelişme takibi ve uzun süreli izleminde görülebilecek hiperlipidemi, obesite, glukoz intoleransı, tip 2 diabet gibi hiperinsülinemiye bağlı komplikasyonların takibi çok önemlidir (9,10).

Bu çalışmada, FM'si olan ve olmayan term yenidoğan bebeklerin ilk iki yaştaki büyümelerinin ve ikinci yaştaki glukoz, insülin ve lipid profillerinin karşılaştırılması amaçlanmıştır.

GEREÇ VE YÖNTEMLER

Hastalar: Çalışmaya Mayıs 2019 ile Ekim 2019 tarihleri arasında Manisa Celal Bayar Üniversitesi Tıp Fakültesi Hafsa Sultan Hastanesi'nde canlı doğan term yenidoğan (son adet tarihine göre gestasyonel yaşı≥38 hafta) bebekler dahil edildi. Çalışma Manisa Celal Bayar Üniversitesi Tıp Fakültesi Sağlık Bilimleri Etik Kurulu'nun onayıyla yapıldı (20.478.486-1130). Çoğul gebelikler, prematüreler (gestasyonel yaşı <37 hafta), ölü doğumlar, annede gebelik öncesi diabet, gestasyonel diabet, hipertansiyon ve erken membran rüptürü olan anne bebekleri çalışmaya alınmadı. Doğumun ardından bebeklerin muayeneleri yapıldı ve ağırlık, boy, baş çevresi ölçümleri yapıldı. Bebekler doğumdan sonraki ilk 12-24 saat içinde aynı çocuk hekimi tarafından CANSCORE yöntemi kullanılarak CANSCORE puanı hesaplandı. CANSCORE yönteminde 9 adet bulgu ve belirti değerlendirmeye alındı. Bebeğin saçına, yanak dolgunluğuna, çene altı yağ dokusuna, kol bacaklarda cilt altı yağ dokusuna, cildin cilt altı dokudan kolay ayrılıp ayrılmadığına, interkostal aralıkta çökmeye, sırtta cilt ve yağ dokusuna, karında cilt altı yağ dokusuna, gluteal bölgede cilt kıvrımlarının sayısı ve derinliğine bakılarak puanlama verildi. CANSCORE yönteminde her bir parametre için minimum 1 (kötü, ileri derecede fetal malnutre) maksimum 4 (iyi, malnütrisyonu olmayan) puan verildi. Değerlendirme sonunda da en az 9; en çok 36 puan elde edilir. CANSCORE puanında sınır değer 24'tür. CANSCORE puanı 24 ve altında olan bebekler FM'si olan bebekler olarak kabul edildi. CANSCORE puanı 24'ten büyük olanlar ise FM'si olmayan bebekler olarak kabul edildi.

Biyokimyasal değerlendirme: Doğumu takiben umblikal kord klempe edildikten sonra umblikal korddan kan örneği alındı. İnsülin, glukoz, total kolesterol, düşük yoğunluklu lipoprotein (LDL), yüksek yoğunluklu lipoprotein (HDL), çok düşük yoğunluklu lipoprotein (VLDL) kolesterol, trigliserid değerleri hemen çalışıldı. Diğer kan örneğini 10 dakika 5000 devirde santrifüj edildikten sonra ayrılan serum örneği leptin, adiponektin, ghrelin düzeyleri çalışılıncaya kadar -80 C□'de MCBÜ Hafsa Sultan Hastanesi Biyokimya Laboratuarında saklandı. Tüm kan örnekleri toplandıktan sonra ayrılan serum örneklerinden ghrelin, leptin ve adiponektin düzeyleri ELİSA kitleri ile çalışıldı.

Büyümenin takibi: FM'si olan ve olmayan bebekler yenidoğan polikliniğinde takibe alındılar ve iki yaşına kadar büyüme ve gelişmeleri takip edildi. Bebeklerin 6., 12., ve 24. ayda vücut ağırlığı, boy uzunluğu, baş çevresi ölçümleri yapıldı, persentil değerleri hesaplandı. Yaşamın ikinci yılında insülin, glukoz, total kolesterol, LDL kolesterol, HDL kolesterol, VLDL kolesterol, trigliserid değerleri çalışıldı.

İstatistiksel analiz: İstatistiksel analiz "SPSS (Statistical Package for Social Sciences) 16.0 for Windows" programı kullanılarak yapıldı. Verilerin değerlendirilmesinde t-testi, ki-kare testi, tek yönlü ANOVA yöntemleri kullanılmıştır. 0.05'ten küçük p değeri istatistiksel olarak anlamlılık kabul edildi.

BULGULAR

Çalışmaya 40 FM'si olan ve 40 FM'si olmayan toplam 80 term yenidoğan bebek alındı. Bu bebeklerden FM'si olan 26 bebek ile FM'si olmayan 22 bebek iki yaşına kadar büyüme ve gelişimleri takip edilebildi. FM'si olan ve olmayan bebeklerin demografik özellikleri incelendiğinde, ponderal indeksi (2,92±0,30 ve 3,18±0,37) ve CANSCORE puanı (20,38±2,24 ve 29,27±3,23) dışında her iki grup arasında anlamlı farklılık bulunmadı (Tablo 1).

Tablo 1. Her iki gruptaki bebeklerin demografik ve antenatal özellikleri ile beslenme şekilleri

	Fetal malnutrisyon (+) (n=26)	Fetal malnutrisyon (-) (n=22)	p
Doğum ağırlığı (g)	3193,46±345,13 (2640-3810)	3411,81±484,45 (2530-4180)	0,076
Doğum boyu (cm)	48,23 ±2,22 (45-52)	48,09±1,65 (45-50)	0,809
Doğum baş çevresi (cm)	34,23±1,66 (31-37)	34,68±2,11 (31-38,5)	0,414
Ponderal indeksi (g/cm³)	2,92±0,30 (2,14-3,49)	3,18±0,37 (2,34-4,24)	**0,001**
Cinsiyet -Kız -Erkek	 10 16	 12 10	0,265
Doğum şekli -NspD -C/S	 2 24	 0 22	0,184
Gestasyonel yaş (hafta)	38,01±1,12 (38-41)	38,42±0,74 (38-40)	0,728
CANSORE puanı	20,38±2,24 (16-23)	29,27±3,23 (25-34)	**<0,001**
Apgar skoru (1.dk)	7(6-9)	8(7-9)	0,192
Apgar skoru (5.dk)	9(8-10)	9(8-10)	1,000
Anne yaşı	32,00±5,38 (22-39)	30,81±4,24(25-39)	0,409
Gebelik sayısı	3 (1-7)	3(1-6)	0,829
Doğum sayısı	2 (1-5)	2 (0-5)	0,530
Gebelikte sigara kullanım oranı	8 (%30,7)	3 (%13,6)	**0,014**
Gebelik öncesi vücut ağırlığı (kg)	71,92±13,77 (52-108)	70,45±11,29 (55-86)	0,692
Gebelik sonundaki vücut ağırlığı (kg)	84,69±13,43 (65-116)	81,72±10,79 (68-97)	0,410

Gebelik boyunca alınan ağırlık (kg)	12,76±6,09 (1-23)	11,27±4,36 (4-18)	0,342
Annenin boyu (cm)	163,69±6,20 (150-178)	158,63±5,15 (150-165)	**0,004**
Annenin vücut kitle indeksi (kg/cm²)	26,74±4,69 (21,40-38,70)	27,95±4,46 (22,60-35,70)	0,368
Vücut kitle indeksine göre			0,593
-Normal (18,5-24,9)	12	8	
-Kilolu (25-29,9)	8	6	
-Obez (>30)	6	8	
Ailenin gelir düzeyi (TL)	2877,50±1777,27 (500-10000)	2458,00±1133,18 (1000-7000)	0,212
Annenin eğitim düzeyi			0,506
-Okur yazar değil	2	1	
-Okur yazar	1	1	
-İlköğretim	13	14	
-Ortaöğretim	3	2	
-Lise	3	2	
-Üniversite	4	2	
Sadece anne sütü alma süresi (ay)	3,85±2,47 (0-6)	5,36±1,50 (2-7)	**0,014**
Toplam anne sütü alma süresi (ay)	8,85±7,16 (1-27)	17,00±7,05 (2-24)	**<0,001**
Ek gıdaya geçiş süresi (ay)	5,69±0,48 (5-6)	6,00±0,44 (5-7)	**0,024**
Formula kullanım oranı	20 (%76,9)	6 (%27,3)	**<0,001**

(NspD: Normal spontan doğum, C/S: sezaryen)

Her iki grubun antenatal öyküsüne bakıldığında anne yaşının iki grupta benzer olduğu görüldü. Annelerin boyları dışında, gebelik öncesi ve gebelik sonundaki vücut ağırlıkları, gebelik sırasındaki alınan ağırlık, doğum sayısı, gebelik sayısı, gelir düzeyi, eğitim seviyeleri ve vücut kitle indeksleri arasında anlamlı farklılık saptanmadı. FM'li bebeklerin annelerinde sigara kullanım oranı anlamlı olarak daha yüksek bulundu (Tablo 1).

Her iki grubun beslenmelerine bakıldığında FM'si olan grupta sadece anne sütü alma süresi, toplam anne sütü alma süresi anlamlı olarak düşük, formula kullanım oranıda anlamlı yüksek bulundu (p=0,014, <0,001, <0,001). Formula kullanım oranı da FM'si olan grupta anlamlı olarak yüksekti (p<0,001) (Tablo 1).

Her iki gruptaki bebeklerin kord kanındaki glukoz değeri FM'si olan gupta anlamlı olarak düşük iken (p=0,002), insülin, HOMA (Homeostasis Model Assesment), kolesterol, LDL kolesterol, HDL kolesterol, VLDL kolesterol ve trigliserid değerleri arasında anlamlı faklılık bulunmadı (Tablo 2).

Tablo 2. Her iki gruptaki bebeklerin doğumda kord kanlarındaki insülin, glukoz, HOMA

	Fetal malnutrisyon (+) (n=26)	**Fetal malnutrisyon (-) (n=22)**
Glukoz (mg/dl)	51,46±14,090 (31-75)	63,18±9,38 (49-80)
İnsülin (mIU/ml)	5,00±3,09 (0,90-13,4)	4,98±3,34 (0,30-9,70)
HOMA	0,70±0,57 (0,08-2,28)	0,80±0,58 (0,04-5,63)
Kolesterol (mg/dl)	63,07±19,61 (34-95)	58,90±22,36 (40-121)
LDL Kolesterol (mg/dl)	28,53±13,40 (8-47)	25,72±21,16 (10-88
HDL Kolesterol (mg/dl)	28,84±8,88 (18-46)	27,63±4,49 (21-36)
VLDL Kolesterol (mg/dl)	5,69±4,12 (2-19)	5,54±4,00 (2-17)
Trigliserid (mg/dl)	28,61±19,67 (12-93)	27,72±19,38 (8-83)

(HOMA: Homeostasis Model Assesment, LDL: Düşük yoğunluklu lipoprotein, HDL: Yüksek yoğunluklu lipoprotein, VLDL: Çok düşük yoğunluklu lipoprotein)

Her iki gruptaki bebeklerin iki yaşındaki kan glukoz, insülin, HOMA, kolesterol, LDL kolesterol, HDL kolesterol değerleri arasında anlamlı faklılık bulunmadı, VLDL kolesterol ve trigliserid değerleri FM'si olan grupta anlamlı olarak daha yüksek bulundu (p =0,015) (Tablo 3).

Tablo 3. Her iki gruptaki bebeklerin iki yaşındaki insülin, glukoz, HOMA ve lipid değerleri

	Fetal malnutrisyon (+) (n=26)	**Fetal malnutrisyon (-) (n=22)**	**p**
Glukoz (mg/dl)	88,30±8,50 (77-108)	94,60±16,13 (81-125)	0,095
İnsülin (mIU/ml)	6,36±4,68 (1,7-14,3)	9,76±14,49 (1,8-49,60)	0,267
HOMA	1,16±0,85 (0,39-3,32)	1,32±1,65 (0,41-5,63)	0,677
Kolesterol (mg/dl)	163,38±29,07 (112-200)	174,70±29,05 (127-211)	0,197
LDL Kolesterol (mg/dl)	90,53±28,59 (44-135)	94,40±31,24 (57-137)	0,665
HDL Kolesterol (mg/dl)	53,38±15,42 (33-88)	51,80±8,16 (40-61)	0,679
VLDL Kolesterol (mg/dl)	19,46±9,52 (7-38)	14,30±5,00 (8-25)	**0,033**
Trigliserid (mg/dl)	97,30±47,99 (33-192)	66,70±27,83 (37-127)	**0,015**

(HOMA: Homeostasis Model Assesment, LDL: Düşük yoğunluklu lipoprotein, HDL: Yüksek yoğunluklu lipoprotein, VLDL: Çok düşük yoğunluklu lipoprotein)

Her iki gruptaki bebeklerin ilk iki yıldaki antropometrik ölçümlerine bakıldığında FM'si olan bebeklerin 6. ayda vücut ağırlığı ve boy uzunluğu anlamlı olarak daha fazla olduğu görüldü, baş çevresi ölçümünde ise anlamlı farklılık saptanmadı. Her iki gruptaki bebeklerin 12. ve 24. aydaki vücut ağırlığı, boy uzunluğu ve baş çevresi ölçümlerinde de anlamlı farklılık saptanmadı (Tablo 4).

Tablo 4. Her iki gruptaki bebeklerin ilk iki yıldaki antropometrik ölçümleri

	Fetal malnutrisyon (+) (n=26)	**Fetal malnutrisyon (-) (n=22)**	**p**
6. ay			
-Vücut ağırlığı (kg)	7,44±1,02 (6-9)	6,52±0,90 (5-8)	**0,002**
-Boy (cm)	66,67±2,80 (62-74)	63,57±1,65 (61-66)	**0,001**
-Baş çevresi (cm)	42,55±2,01 (39-45)	42,07±1,39 (41-44)	0,448
12. ay			
-Vücut ağırlığı (kg)	10,19±1,00 (9-12)	9,60±1,32 (6-11)	0,085
-Boy (cm)	76,50±3,50 (73-85)	76,00±2,00 (74-79)	0,709
-Baş çevresi (cm)	46,22±1,86 (42-49)	45,25±1,16 (44-47)	0,189
24. ay			
-Vücut ağırlığı (kg)	12,56±1,66 (10-15)	12,02±1,65 (9-14)	0,275
-Boy (cm)	84,10±3,35 (80-91)	84,13±3,20 (80-90)	0,982
-Baş çevresi (cm)	48,78±1,92 (46-53)	48,33±1,67 (47-51)	0,920

Ağırlık, boy ve baş çevresi persentillerinde ise iki grup arasında 6., 12. ve 24. aylara arasında farklılık saptanmadı (Tablo 5).

Tablo 5. Her iki gruptaki bebeklerin ilk iki yıldaki büyüme persentilleri

	Fetal malnutrisyon (+) (n=26)	Fetal malnutrisyon (-) (n=22)	p
6. ay vücut ağırlığı			
<3persentil	4	6	0,256
3-97persentil	22	16	
6. ay boy			
<3persentil	4	4	0,218
3-97persentil	19	18	
>97 persentil	3		
6. ay baş çevresi			
<3persentil	4	0	0,091
3-97persentil	22	22	
12. ay vücut ağırlığı			
<3persentil	0	2	0,055
3-97persentil	22	20	
>97 persentil	4	0	
12. ay boy			
3-97persentil	24	22	0,353
>97 persentil	2	0	
12. ay baş çevresi			
<3persentil	2	0	0,471
3-97persentil	24	22	
24. ay vücut ağırlığı			
<3persentil	0	2	0,131
3-97persentil	26	20	
24. ay boy			
<3 persentil	3	2	0,829
3-97persentil	23	20	
24. ay baş çevresi			
3-97persentil	24	22	0,232
>97 persentil	2	0	

TARTIŞMA VE SONUÇ

Fetusun büyümesi, genetik, maternal faktörler, intrauterin ortam, maternal ve fetal hormonlar tarafından düzenlenen karmaşık bir süreçtir (11). Fetal malnütrisyon, intrauterin büyüme kısıtlılığının (İUBK) en sık nedenidir. İUBK'nın etiyolojisi komplekstir, fetal beslenme problemlerinin en yaygın tipidir (12). Tüm düşük doğum ağırlıklı bebekler İUBK olmadığı gibi tüm İUBK olan bebeklerde düşük doğum ağırlıklı değildir (13). FM'yi saptamak için term bebeklerde klinik özelliklere göre CANSCORE yöntemi kullanılır (14). FM herhangi bir doğum ağırlığında ortaya çıkabilir. FM'si olan bir bebeğin vücut ağırlığı, boyu ve baş çevresi normal sınırlarda olabilir ya da olmayabilir (1). Çalışmamızda FM'si olan bebeklerin doğum ağırlıkları, boyu ve baş çevresi normal sınırlardaydı. FM'si olan ve olmayan bebeklerin de doğum ağırlıkları, boyu ve baş çevresi arasında anlamlı farklılık yoktu.

FM'nin kalıcı yapısal ve fonksiyonel değişikliklere yol açtığı varsayıldığında düşük doğum ağırlığı ile endokrinometabolik patalojiler arasındaki ilişki dikkat çekmektedir. Barker hipotezi olarak bilinen bu ilişki birçok epidemiyolojik çalışma ile de doğrulanmıştır (9,15,16). Postnatal dönemdeki hızlı büyüme, ileri yaşlardaki patolojilerin ortaya çıkmasında önemli bir faktördür. İntrauterin büyüme kısıtlılığı olan bebekleri postnatal dönemdeki büyümesi ve kilo alımları gelecekteki sağlık durumlarının temel belirleyicidir (6,7).

Fetal büyüme kısıtlılığı, fetüsün yağ dokusunun doğru bir şekilde oluşmasını engeller ve metabolik fonksiyonlarını, endokrin salgılarını ve bunun sonucunda ekstrauterin metabolik adaptasyonunu bozabilir. İUBK olan bebeklerde ileri yaşlarda insülin direnci ve bozulmuş glukoz metabolizması ortaya çıkabilir (17). Bu bebekler yaşamın ilerleyen dönemlerinde obesite, insülin direnci ve bununla ilişkili metabolik bozuklukların gelişimine daha yatkındır (18). Epidemiyolojik çalışmalar, İUBK'nın neden olduğu düşük doğum ağırlığı ile erişkin dönemde glisemik metabolizma bozukluklarıve diyabet arasında bir ilişki olduğunu göstermiştir (19).

Bizim çalışmamızda FM'si olan ve olmayan bebeklerin kordon kanındaki glisemik profiline baktığımızda FM'si olan bebeklerde glukoz değeri anlamlı olarak daha düşüktü, insülin ve HOMA değerleri arasında ise anlamlı farklılık yoktu. FM'si olan bebeklerde saptadığımız kan glukoz düşüklüğünün, glikojen tüketiminde artışın yanısıra, düşük glukoneojenik hız nedeniyle glukoz gereksinimindeki artıştan dolayı olabileceği düşünüldü. Yaşamının ikinci yılında FM'si olan ve olmayan bebeklerin glukoz, insülin ve HOMA değerleri arasında farklılık yoktu.

Larruscain ve arkadaşlarının çalışmasında İUBK olan ve büyümeyi yakalayanlarda, büyümeyi yakalayamayan bebeklere göre kord kanındaki glukoz değerlerinin anlamlı olarak düşük olduğu görülürken, insülin ve HOMA değerleri arasında ise anlamlı farklılık saptanmamış, yaşamlarının 9. ve 12. aylarındaki glukoz, insülin ve HOMA değerleri arasında anlamlı farklılık bulunmamıştır (20). Yapılan başka çalışmalarda da İUBK olan bebeklerin 12. aydaki glukoz ve insülin düzeylerinde farklılık saptanmamıştır (21,22).

Fetal büyüme ve yağ dokusunun yapısının gelişmesinde görevli hormonlar dışında kolesterol ve indirekt etki ile trigliserid oldukça önemlidir. Yapılan çalışmalarda intrauterin gelişme geriliği olan bebeklerin kord kanında kolesterol ve trigliserid düzeyi anlamlı olarak düşük bulunmuştur (23). Bizim çalışmamızda her iki grubun kordon kanındaki kolesterol ve trigliserid düzeyleri arasında anlamlı farklılık saptanmadı.

Garcia ve arkadaşlarının çalışmasında da olduğu gibi fetal gelişim parametreleri ile kord kanındaki lipid profili arasındaki korelasyonla ilişkili farklı kanıtlar bulunmaktadır (24). Garcia ve arkadaşlarının çalışmasında intrauterin gelişme geriliği olan bebeklerin doğumdaki lipid değerleri ile doğumdaki antropometrik ölçümler arasında ilişki olmadığı gösterilmiştir (24). Bu ilişkinin olup olmaması daha sonraki dönemde gelişebilecek metabolik bozuklukları önceden tahmin etmemizi sağlamamaktadır (25).

İUBK ile doğan bebeklerde değişmiş lipid düzeylerinin gelecekteki etkileri bilinmemekle birlikte, yenidoğan VLDL kolesterol ve LDL kolesterol düzeylerinin 13 yaşındaki düzeyleri öngördüğünü belirtmek ilginçtir (26). Fetal programlamayı destekleyen kanıtlar ve çalışmalar İUBK ile doğan bebeklerde lipid ve diğer kardiyovasküler risk faktörlerini araştırmaktadır. Sonuçta, fetal lipidler İUBK ile komplike olan gebeliklerde değişmektedir. Bu bulgular, bu bebeklerin gelecekteki kardiyovasküler sağlığı için

potansiyel etkilere sahiptir (27). Leunissen ve arkadaşlarının yapılan gözlemsel bir çalışmasında fetal büyüme geriliği olan bebeklerde yaşamın ilk üç ayında hızlı kilo alımı olduğunda, erken yetişkinlikte daha düşük HDL kolesterol düzeyleri ve daha yüksek total kolesterol/HDL kolesterol indeksi olduğu saptanmıştır (28). Bu çalışmada, yaşamın ilk yılında, total kolesterol, LDL ve HDL kolesterol düzeyleri, büyüme persentilini yakalayan ve yakalamayan fetal büyüme geriliği olan her iki grupta da benzer bulunmuştur. Soto ve arkadaşlarının çalışmasında da büyüme persentilini yaklayan ve yakalamayan İUBK bebeklerin kolesterol düzeylerinde istatistiksel olarak anlamlı bir fark bulunmamıştır (21). Larruscain ve arkadaşlarının çalışmasında da İUBK olan ve büyümeyi yakalayan ve yakalamayan bebeklerin 3., 6. ve 12. aydaki total kolesteol, LDL ve HDL kolesterol değerleri arasında anlamlı farklılık saptanmamıştır (20). Bu nedenle, kolesterol düzeyleri, en azından erken aşamalarda gelecekteki endokrinometabolik patolojinin iyi bir göstergesi gibi görünmemektedir (20).

Çalışmamızda FM'si olan ve olmayan bebeklerin iki yaşındaki total kolesterol, LDL koesterol ve HDL kolesterol düzeyleri arasında anlamlı farklılık saptanmadı. FM'si olan bebeklerde, FM'si olmayan bebeklere göre iki yaşındaki VLDL kolesterol düzeyi anlamlı olarak daha yüksek bulundu. Bu bebeklerin kord kanındaki VLDL kolesterol düzeyleri anlamlı olmasa da daha yüksek olduğu ve ilk 6 aydaki kilo alımının daha hızlı olduğu görülmektedir. Bununla birlikte VLDL kolesterolün, LDL kolesterolün öncüsü olması FM'si olan bebeklerde erken çocukluk dönemindeki VLDL kolesterol düzeyinin ileri yaşlardaki kardiovasküler hastalıklar açısından yol gösterici olabilir (29).

FM'si olan bebeklerin VLDL kolesterol dışında trigliserid düzeyi de anlamlı olarak daha yüsek saptandı. FM'si olan bebeklerin, FM'si olmayan bebeklere göre yaşamının 6. ayında daha hızlı kilo aldığı ve bu bebeklerin yaşamının ikinci yılında daha yüksek trigliserid değerlerine sahip olduğu saptandı. Yapılan çalışmalarda, serum trigliserid düzeyinin insülin direncinin iyi bir göstergesi olduğu kabul edilmektedir (30). Bizim çalışmamızda da postnatal erken dönemde hızlı kilo artışı olan bebeklerdeki anlamlı trigliserid yüksekliğinin saptanması, bu bebeklerin ileri yaşlarda insülin direncine eğilimlerinin olabileceğini düşündürmüştür.

Larruscain ve arkadaşlarının çalışmasında, İUBK olan bebeklerden büyümeyi hızlı yakalayanların, 12. ayda trigliserid değerlerinin anlamlı olarak daha yüksek olduğu saptanmıştır (20). Leunissen ve arkadaşlarının çalışmasında da ilk 3 ayında hızlı kilo alan İUBK bebeklerin erken erişkin dönemde daha yüksek trigliserid değerlerine sahip olduğu görülmüştür (28). Sotto ve arkadaşları da İUBK olan bebeklerin birinci yaşında trigliserid değerlerinin kontrol grubuna göre daha yüksek olduğunu göstermişlerdir (21).

Çalışmamızda FM'si olan ve olmayan bebeklerin ilk iki yaşdaki antropometrik ölçümlerine baktığımızda, 6. ayda FM'si olan bebeklerin vücut ağırlığı ve boy uzamasının FM'si olmayan bebeklere göre daha fazla olduğu görüldü. 12. ve 24. ayda ise vücut ağırlığı, boy ve baş çevresi ölçümleri arasında anlamlı farklılık bulunmadı. 6., 12. ve 24. aylardaki büyüme persantillerinde ise her iki grup arasında farklılık yoktu. Çalışmamızdaki FM'si olan bebeklerin erken dönemde hızlı kilo artışı, bu bebeklerde formula kullanım oranındaki yüksekliği ve anne sütü alma süresinin kısalığı ile ilişkilendirildi.

Sonuç olarak, FM'li bebeklerde yaşamının ilk 6 ayındaki hızlı kilo artışı erken çocukluk dönemindeki lipid profilini etkileyebilmektedir. FM'si olan bebeklerin erken çocukluk döneminde saptanan trigliserid ve VLDL kolesterol yüksekliği, metabolik sendrom için yol gösterici olabilir. Doğum ağırlıkları normal olsa bile FM saptanan bebeklerin doğumdan sonra, özellikle de ilk 6 aydaki büyümesi yakın takip edilmeli ve ileri yaşlarda gelişebilecek metabolik bozukluklar açısından dikkatli olunmalıdır.

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Comparison of perioperative outcomes for endometrial cancer staging via traditional laparotomy, laparoscopy and robotic-assisted surgery: short term initial experience.

Geleneksel laparotomi, laparoskopi ve robot yardımlı cerrahi ile endometrial kanser evrelemesinin perioperatif sonuçlarının karşılaştırılması: kısa süreli ilk deneyim

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ÖZ

Amaç:Bu çalışmanın amacı, dünyada ve Türkiye'de en sık görülen jinekolojik kanser türü olan endometrium kanseri evrelemesinde geleneksel abdominal histerektomi (TAH), total laparoskopik histerektomi (TLH) ve robotik yardımlı histerektominin (TRH) perioperatif sonuçlarını karşılaştırmaktır.

Gereç ve yöntemler: Çalışmada endometriyal kanser nedeniyle evreleme cerrahisi yapılan 58 hasta dahil edildi. Tüm olgular Şubat 2015-Mayıs 2016 tarihleri arasında aynı jinekolojik onkolog (E.B.) tarafından Sağlık Bilimleri Üniversitesi Adana Numune Eğitim ve Öğretim Hastanesi'nde opere oldu. Primer sonuç ölçütü perioperatif komplikasyonlardı. İkincil sonuç ameliyat süresi, ameliyat sonrası hemoglobin düşüşü, kan transfüzyon oranları ve hastanede kalış süresi idi.

Bulgular:23 olgu laparotomi, 10 olgu laparoskopi ve 25 olgu robotik asiste olmak üzere 3 grup belirlendi. Gruplar arasında yaş, parite, derece ve miyometrial invazyon derinliği açısından istatistiksel olarak anlamlı fark yoktu. Genel komplikasyon oranı TAH grubunda daha yüksekti. TRH ve TLH hastalarında, TAH hastalarına kıyasla böbrek yetmezliği, idrar yolu enfeksiyonu ve ameliyat sonrası ateş görülme olasılığı daha düşüktü. TRH grubundaki hemoglobin düşüşü diğer gruplardan daha azdı fakat istatisiksel olarak anlamlı değildi (p= 0,797). Ortalama ameliyat süresi TRH olgularında TLH ve TAH olgularına göre daha uzundu (sırasıyla 300, 230, 165 dakika). TAH, TLH ve TRH hastalarının ortanca hastanede kalış süreleri sırasıyla 5, 3 ve 2 gündü (p < 0.0001). Minimal invaziv cerrahi gruplarında (TLH'de 0/10 vaka ve TRH'de 3/25 vaka) geleneksel yaklaşımlardan (TAH'da 5/23 vaka) önemli ölçüde daha az kan transfüzyonu gereksinimi vardı.

Sonuçlar: Kısa vadeli ilk deneyimlerimizle, minimal invaziv cerrahi yaklaşım üstün perioperatif sonuçlarla sonuçlandı. Daha uzun ameliyat sürelerine rağmen, bu çalışmadan elde edilen sonuçlar endometriyum kanserinin tedavisinde robot yardımlı cerrahi evrelemenin hem uygulanabilir olduğunu hem de daha kısa hastanede kalış süresi ile ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: Endometriyal kanser; Laparoskopik cerrahi; Robotik cerrahi; Perioperatif komplikasyonlar

ABSTRACT

Aim: To compare the perioperative outcomes of traditional abdominal hysterectomy (TAH), total laparoscopic hysterectomy (TLH), and robotic-assisted hysterectomy (TRH) for endometrial cancer staging, which is the most common gynecological cancer type in Turkey Materials and Methods: All cases were performed by the same gynecologic oncologist (E.B.) from February 2015 to May 2016 in Adana Numune Education and Training Hospital. The study was conducted retrospectively. The primary outcome measure was perioperative complications. The secondary outcome measures were operative time, postoperative hemoglobin drop, blood transfusion rates and length of the hospital stay

Results: 23 cases were laparotomy (TAH), 10 cases were laparoscopy (TLH), and 25 cases were robotic-assisted (TRH) There were no statistically significant differences between the groups in terms of age, parity, grade and depth of myometrial invasion. The overall complication rate was higher in the TAH group.TRH and TLH patients were less likely to have renal failure, urinary tract infection and postoperative fever compared to TAH patients. The decrease in hemoglobin in the TRH group was less than in the other groups, but it was not statistically significant (p= 0.797).Mean operative time was longer in TRH cases than in TLH and TAH cases (300, 230, and 165 minutes, respectively).The median lengths of hospitalization for TAH, TLH, and TRH patients were 5, 3, and 2 days, respectively (p < 0.0001) There were significantly fewer blood transfusion requirements in minimally invasive surgery groups (0/10 case in TLH and 3/25 cases in TRH) than in traditional approaches (5/23 cases in TAH)

Conclusions: With our short term initial experience, minimally invasive surgical approach resulted in superior perioperative outcomes. Despite longer operative times, the results from this study suggest that robotic-assisted surgical staging in the management of endometrial cancer is both feasible and associated with a shorter length of hospitalization.

Keywords: Endometrial cancer; Laparoscopic surgery; Robotic surgery; Perioperative complications

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INTRODUCTION

Endometrial cancer is the second most common gynecologic malignancy worldwide and the most common in Turkey. According to the results of the World Health Organization (WHO) for 2020, endometrial cancer ranks 5th at 5.9% in terms of the number of new cases among women of all ages in Turkey (1). Endometrial cancer is the most commonly diagnosed type of gynecological cancer in Turkey, occurring at a median age of 58 years (2). During this period, the average incidence of uterine cancer was 10.36 per 100,000, or 3851 new cases per year (2).

The way cancers are staged has evolved over the last 70 years to keep pace with the rapid growth of medical research and practice, particularly in oncology (3). According to FIGO (The International Federation of Gynecology and Obstetrics) decisions from 1988, the laparotomy approach is the traditional method for surgically staging endometrial cancer (4, 5). Along with the early diagnosis, proper staging surgery is critical for the disease's prognosis. A total extra-facial hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic-paraaortic lymph node dissection (PPLND) are the standard surgical methods for diagnosing and treating endometrial cancer, but there are many other options (6). Additional surgical approaches include vaginal, TLH, or TRH staging. After Reich et al. (7) published TLH hysterectomy cases in 1988, Dargent et al. (8) described TLH lymphadenectomy in gynecological malignancies in 1989. In 1991 and 1993, Querleu et al. (9, 10) published about the first time they did a transperitoneal pelvic lymphadenectomy on 39 people with cervical cancer. Nezhat et al. (11) published the first TLH paraaortic lymphadenectomy in 1992. Today, the widespread use of TLH in many areas has also aided in the advancement of laparoscopy in gynecological oncology (12). Studies and meta-analyses show that the use of TLH in the staging and treatment of endometrial cancer reduces perioperative morbidity, shortens hospital stay, and has similar efficacy, mean survival, and disease-free survival compared to TAH (13). This is because TLH applications have some problems, like limited mobility and poor image quality. TRH was born out of this desire to do the best job possible with the least amount of surgery (14). In Turkey, Göçmen et al. (15) reported in a study published that TRH enables three-dimensional imaging and more comfortable movement, allowing for the endoscopic treatment of more complex cases. Despite these advantages, TRH surgery has several disadvantages, including a lack of tactile sense, long setup time, and high cost.

This study was to compare the perioperative results of patients who underwent TAH, TLH, TRH, and staging surgery with the diagnosis of endometrial cancer in our clinic. This study's aim was to compare the perioperative results of patients who underwent TAH, TLH, TRH, and staging surgery with the diagnosis of endometrial cancer in our clinic. On the other hand, we aimed to determine whether TLH and TRH, as minimally invasive surgical methods, have superiority over each other in terms of perioperative results.

MATERİAL AND METHODS

Our study was planned as a retrospective cross-sectional analysis, and included 23 TAH, 10 TLH, and 25 TRH patients who were operated on for endometrial cancer in the Department of Obstetrics and Gynecology of Health Sciences University Adana Numune Training and Research Hospital between February 2015 and May 2016. The procedures were in accordance with the ethical standards set by the responsible human experimentation committee (institutional and national) and 1975 Helsinki Declaration. The inclusion criteria specified that participants must be between the ages of 18 and 85 and have undergone endometrial cancer surgery. The criterion for exclusion was the presence of synchronous cancers. We received approval for the study from the Ethics Committee of Adana Numune Training and Research Hospital, University of Health Sciences, on June 28, 2016, with decision number 95.

Endometrial biopsy with a Pipelle curette is often sufficient for diagnosis in patients with suspected endometrial cancer. However, false negative rates of Pipelle curette endometrial biopsy are reported to be 10%. For this reason, in symptomatic patients with a strong suspicion of endometrial cancer, we make the diagnosis in our clinic with fractionated dilatation and curettage (16). Transvaginal ultrasonography and chest radiography were found to be sufficient for the initial evaluation of patients with endometrioid type histology. Advanced radiological evaluations (magnetic resonance imaging, computed tomography) were performed in the presence of suspected extrauterine spread (17). Ca-125 and whole-body computed tomography were added to the preoperative evaluation to see if there was a spread outside of the uterus (18).

We staged endometrial cancer according to the 2009 FIGO staging system. Primary treatment included surgical staging, and we planned adjuvant treatment according to the stage of the disease. Total hysterectomy and BSO, which are the recommended approach in grade 1-2 patients with endometrioid type histology preoperatively, were performed. It was decided whether we should send the specimen for frozen pathological evaluation and lymph node dissection should be performed according to the risk factors for extra-uterine spread (19, 20). Due to the increased risk of extrauterine spread in patients with non-endometrioid histology or grade 3 endometrioid histology, a complete staging surgery was performed, including abdominal hysterectomy, BSO, omentectomy, and bilateral PPLND (21). In the case of intra-abdominal spread, cytoreductive surgery procedures like those used for ovarian cancer were thought about, with the goal of leaving no tumor behind (22, 23). At the time of admission, patients who were diagnosed with endometrial cancer because of Lynch syndrome were excluded from the study. One gynecologic oncology surgeon with TRH experience performed all necessary robotic surgeries using the da Vinci® Si HD - Cordamed surgical system. Two gynecological oncology surgeons and one obstetrician and gynecologist performed the TLH and TAH procedures. The surgical technique was decided in collaboration with other gynecological oncology specialists during an oncology council meeting during which each patient was presented prior to surgery. As a result of the meeting, it was determined that the patient was not a candidate for minimally invasive surgery, and the same surgical team performed the open procedure (24).

Age, number of children, type of endometrial cancer, type of surgery performed, grade and stage of the tumor, number of pelvic-paraaortic lymph nodes, duration of operation, adverse events, length of hospital stay, and complete blood count chan-

ge (preoperative compared to postoperative hemoglobin) were all collected. The operative time was calculated as the time from the surgeon initiating the skin incision to the wound line being closed. The time spent in the theatre was tracked from the time the patient entered to the time they exited. All patients met the same discharge criteria: they restored their mobility without help, tolerated a restricted diet, and maintained pain control with oral medications.

Statistical analysis

The IBM SPSS for Windows V24.0 package program was used to analyze the data. The Shapiro-Wilk test was used to determine whether the variables were suited for normal distribution. The mean and standard deviation were used to highlight variables that met the assumption of normal distribution, while the median (minimum–maximum) was used to summarize variables that did not meet the assumption. Numbers and percentages were used to summarize categorical variables. The cross tables were analyzed using the chi-square test. When the normal distribution condition was not met in group comparisons, the Kruskal-Wallis test was used to detect the difference between more than two groups, and Dunn's test was used to discover which groups contributed to the difference. In the case where the assumption was provided, the ANOVA test was used. The statistical significance level of $p < 0.05$ was accepted.

RESULTS

As shown in Table 1, there is no significant difference in mean age among the TAH, TLH, and TRH groups (p=0.57).

Table 1. Age and parity characteristics of the groups.

	TAH (n=23)	TLH (n=10)	TRH (n=25)	p value
Age	60.6 ± 11.6	62.6 ± 9.5	58.4 ± 10.8	0.57
Parity	3 (2 – 5)	3 (0 – 4)	3 (2 – 4)	0.59

The statistical analysis was performed with Chi-Square analysis

As shown in Table 2, there is no significant relationship between the grade and the groups (p=0.270) and the degree of myometrial invasion and the groups (p=0.738)., there is a significant difference between the groups in terms of the number of pelvic lymph nodes (p<0.001). The TAH group differed significantly from the other groups in terms of the number of paraaortic lymph nodes and total lymph nodes count (p<0.05 and p<0.001, respectively) in

Table 2. Distribution of the groups by the grade, the degree of myometrial invasion and the number of lymph nodes

	TAH	TLH	TRH	p value
Grade1 (n, %)	12 (54.5%)	3 (30%)	13 (52%)	0.270
Grade2 (n, %)	7 (31.8%)	7 (70%)	8 (32%)	
Grade3 (n, %)	4 (13.6%)	-	4 (16%)	
Myometrial invasion depth less than 50%	13 (56%)	7 (70%)	16 (64%)	0.738
Myometrial invasion depth more than 50%	10 (43%)	3 (30%)	9 (36%)	
Total Lymph Nodes Count (min.-max.)	42 (11 – 66) *	20 (6 – 43)	21.5 (13 – 38)	**< 0.001**
Paraaortic Lymph Nodes Count (min.-max.)	11(3 – 22)	4 (0 – 23)	5 (3 – 8)	**0.005**

The statistical analysis was performed with Chi-Square analysis. *Dunn's test was applied to determine the group that made the difference

As shown in Table 3, the operative times are the longest in the TLH group and the shortest in the TAH group (p<0.001). The length of hospital stay was the shortest in the TRH group and the longest in the TAH group (p<0.001).

Table 3. The distribution of the groups in terms of operation time, hospital stay, and hemoglobin amount decreases.

	TAH (n=23) median (min.–max.)	TRH (n=25) median (min.–max.)	TLH (n=10) median (min.–max.)	p value
Operation time (min.)	165 (110 – 335)*	230 (150 – 390) *	300 (240 – 380) *	< 0.001
Length of hospital stay (days)	5 (3 – 8)*	2 (2 – 4)	3 (3 – 4)	< 0.001
hemoglobin change (g/dl)	1.2 (0.40 – 3.20)	1.1 (0.30 – 3.30)	1.6 (0.70 – 2.0)	0.797

The statistical analysis was performed with one-way ANOVA *Dunn's test was applied to determine the group that made the difference

As shown in Table 4, considering all groups, 55.2% of the patients who are operated on in our clinic were considered to be in stage IA, while 24.1% are considered to be in stage IB.

Table 4. Distribution of groups according to stages..

	TAH (n= 23) (n, %)	TRH (n=25) (n, %)	TLH (n=10) (n, %)	Total (n, %)
IA	11 (47)	14 (56)	7(70)	32 (55.2)
IB	5 (21)	6 (24)	3 (30)	14 (24.1)
II	3(13)	2 (8)	-	5 (8.6)
IIIA	3 (13)	-	-	3 (5.1)
IIIB	-	1 (4)	-	1 (1.7)
IIIC2	1 (7)	2 (8)	-	3 (5.1)

The statistical analysis was performed with Chi-Square analysis

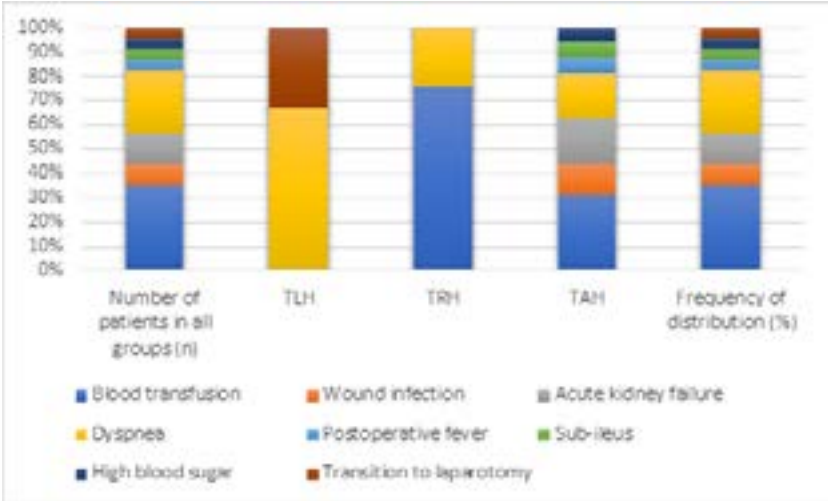
Table 5 and Figure 1 show that complications are frequently seen in the TAH group.PPLND performed in patients in the TAH group increases the risk of bleeding since itis a more invasive surgical intervention than minimally invasive surgical techniques. The large surgical incision area in the TAH group, it brings with it an increase in thenumber of postoperative wound infections. The frequency of acute kidney injury,increased need for blood transfusion, and dyspnea is more common in patients whounderwent TAH, as expected.

Table 5. Complication distributions in all groups

Patients with complications	Number of patients in all groups (%)	TLH (%)	TRH (%)	TAH (%)
No complication	35 (60,3)	-	-	-
Blood transfusion	8(13,8)	-	3 (5.1)	5 (8.6)
Wound infection	2 (3,4)	-	-	2 (3.4)
Acute kidney failure	3 (5,2)	-	-	3 (5.1)
Dyspnea	6 (10,3)	2 (3.4)	1(1,7)	3 (5.1)
Postoperative fever	1(1,7)	-	-	1 (1,7)
Sub-ileus	1 (1,7)	-	-	1 (1,7)
High blood sugar	1 (1,7)	-	-	1 (1,7)
Transition to laparotomy	1(1,7)	1 (1,7)	-	-

The statistical analysis was performed with one-way ANOVA

Figure 1. Complication distributions in all groups



Traditional abdominal hysterectomy (TAH), Total laparoscopic hysterectomy (TLH), and Roboti-c-assisted hysterectomy (TRH)

DISCUSSION

In our study, three available surgical methods were examined in terms of their perioperative results. Since including TRH into the practice of gynecological oncology, the patient group that benefits most from this technology is patients with endometrial cancer. Along with overcoming many of the limitations of traditional TLH, TRH has elevated minimally invasive approaches in gynecological oncology to a new level (25). We know that since most of these patients are obese; they are more prone to complications caused by traditional TAH approaches. Obesity is not only a known risk factor for endometrial cancer, but it also has a big impact on the surgery that is chosen (26). According to the authors, in a study that included obese and morbidly obese endometrial cancer patients and compared TRH and TLH staging, TRH was performed with a shorter operation time, decreased blood loss, increased total lymph node count, and shorter hospital stay in both obese and morbidly obese patient groups (27).

Although TLH staging of endometrial cancer results in less blood loss and faster recovery times, staging has limitations. A longer learning curve for the surgeon, a longer operation time than the TAH approach, and the surgeon's inability to perform complex surgery are some drawbacks of this method (28). According to studies, the learning curve for laparoscopic endometrial cancer surgery is between 20 and 100 cases, allowing the surgeon to achieve a stable operation time and enough lymph node excisions (25). Also, it has been shown that different TLH techniques influence the rates of morbidity and recurrence of tumoral tissue in the vaginal cuff (25).

The da Vinci® Si HD System has many advantages over conventional laparoscopy. Among these are the short learning curve, the 3-dimensional vision it provides in the

surgical field, the articulation of the instruments used, and the surgeon's movement

without force can be considered (29). When we look at the publications comparing the TRH approach and the TAH approach in endometrial cancer surgery, although TRH has longer operation times, it is seen that it has advantages such as less blood loss, reduced transfusion needs, a decrease in complication rates, and shorter hospital stays (30). When compared in terms of lymph node numbers, it was seen that TRH with a laparoscopic approach had similar lymph numbers (31). Due to the shorter learning curve of TRH compared to laparoscopic endometrial cancer surgery, it has found a chance to be widely used in a short time. When compared with both TAH and TLH staging, it has been shown that TRH staging surgery causes less morbidity, especially in the obese patient group (32).

The median age at diagnosis of endometrial cancer is 60 years in the USA (33). In our study, the mean age at diagnosis was 60 in the TAH group, 58 in the TLH group, and 62 in the TRH group. There was no significant difference in age values between the groups ($p = 0.570$). According to the hemogram results on the postoperative first day, the mean decrease in hemoglobin was 1.6 g/dl in the TLH group, 1.2 g/dl in the TAH group, and 1.1 g/dl in the TRH group. TRH patients lost less blood than all other groups. This is in line with the existing literature. In the TLH group, blood loss can be attributed to a surgeon learning curve, fewer patients in that group, and fewer high-resolution images in laparoscopic surgery than in TRH.

In our study, there is a significant difference between the groups in terms of operation time values ($p < 0.001$). Considering that the preparation period was included in the operation times in the TRH group, we observed that the operation time was much shorter compared to the TLH group. Considering that the mean age of patients with endometrial cancer is 60, we would like to point out that there is a shorter staging time in TRH than in TLH due to the accompanying problems in etiology and obesity. In the TRH group, the patient stays in the Trendelenburg position for less time and anesthesia-related complications are less common.

In our study, we found that there was a big difference in the number of totals, pelvic, and paraaortic lymph nodes between the groups ($p<0.001$, $p<0.001$, and $p=0.05$, respectively). While the median total lymph count was 42 in the TAH group, it was calculated as 21.5 in the TLH group and 20 in the TRH. It is well known that the most important oncological parameter in staging surgery is the total lymph count (32). Depending on the learning curve of the surgeon in TRH and TLH operations, there are studies in the literature (34) in which the total number of lymph nodes in TRH is high. The learning curve of the surgeon, different evaluations among pathologists, and the earlier stage of endoscopic patient groups compared to the TAH group can be counted among the reasons for the low number of total lymph nodes in the patient group we performed minimally invasive surgery (35).

In our study, no complications were observed in 60.1% of the patients. Among all groups, 2/3 of the existing complications were observed in the TAH staging group. Our findings were compatible with studies in the literature (32). Three patients in our TAH group were followed up because of impaired renal function tests after surgery. Since wound infection developed in 2 patients in our TAH group, they were hospitalized again after discharge. Due to the development of ileus in 1 patient in the TAH group, postoperative follow-up was performed. The need for blood transfusion was observed at a rate of 5.4% in all patients. Of the eight patients who needed blood transfusions, five were in the TAH group and three were in the TRH group. It was found that none of the patients in the TLH group needed transfusions, and the highest blood transfusion was used in the TAH group, which is consistent with the current literature (32). While an equal number of patients were observed in the TAH and TRH groups due to postoperative dyspnea, dyspnea was observed in only 1 patient in the TLH group. We believe the low number of patients, as well as the advantages of minimally invasive surgery, are among the reasons for the low complication rates in the laparoscopy group. There is a significant difference between the groups in terms of hospitalization duration values ($p<0.001$). While the longest hospitalization period was observed in the TAH group, the shortest hospitalization period in the TRH group is consistent with the current literature (25).

Limitations:

The study's limitations include the fact that it was conducted in a single center and with a relatively small sample size. Additionally, the limited sample size impairs the statistical analysis and limits the generalizability of the findings. Future studies should also include long-term follow-up to find out how long patients live and how they feel about their lives. Our study could not be extended to a long period in the TRH group due to the high costs and the intensity in the hospital operating room.

CONCLUSION

TRH is an advantageous method in gynecological oncology with its high 3D image quality, the quality of surgical equipment brought by minimally invasive surgery, patient satisfaction with pain, and lower postoperative complications compared to TAH. Considering the postoperative complications, patient safety, need for blood transfusion and length of stay in hospital, minimally invasive surgery and especially TRH will find more place in endometrial cancer surgery in the future. More prospective studies are needed on the results of TRH in endometrial cancer surgery.

Conflict of Interest:

The authors declared no conflict of interest.

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Özgün Araştırma / Original Article

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Comparison of First and Third Trimester Complete Blood Count Parameters for Prediction of Preterm Birth

Preterm Doğum Öngörüsünde Birinci ve Üçüncü Trimester Tam Kan Sayımı Parametrelerinin Karşılaştırılması

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ÖZ

Amaç: Tam kan sayımı parametreleri ve nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), ortalama trombosit hacmi (MPV) gibi bu parametrelerin kombinasyonları inflamatuar belirteçlerdir. Bu çalışmada tam kan sayımı parametrelerinin (NLR, PLR ve MPV) erken doğumu tahmin etmedeki olası rolünü değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Birinci ve üçüncü trimesterdeki tam kan sayımı parametreleri kaydedildi ve NLR, PLR değerleri hesaplandı. Çalışma popülasyonu preterm doğumlar (n=94) ve miadında doğumlar (n=953) olarak kategorize edildi. Preterm doğum grubu ayrıca erken preterm (n=11) ve geç preterm (n=83) olmak üzere iki subgruba ayrıldı. İnflamatuvar belirteçler çalışma grupları arasında birinci ve üçüncü trimester için ayrı ayrı karşılaştırıldı. Ayrıca birinci ve üçüncü trimester değerleri arasındaki değişimler de değerlendirildi.

Bulgular: İlk trimester değerleri çalışma grupları arasında benzerdi. Birinci ve üçüncü trimesterler arasındaki MPV değişimi, preterm grupta term gruba göre anlamlı olarak daha düşüktü (0.0 ± 1.1 vs. 0.2 ± 1.1, p = 0.038). Ayrıca birinci ve üçüncü trimesterde NLR değerleri erken preterm subgrupta geç preterm ve term gruplara göre daha yüksekti (ilk trimester; 4.0 ± 1.2 vs. 3.1 ± 2.0 and 3.1 ± 1.3, p = 0.005; üçüncü trimester; 5.3 ± 1.2 vs. 4.0 ± 1.5 and 4.4 ± 2.9, p = 0.013).

Sonuç: NLR ve MPV ilk trimester ve doğum öncesinde preterm doğumları öngörmektedir. Bu da hekimlerin preterm doğumu önlemek için bazı önlemler almasını sağlar.

Anahtar kelimeler: Tam kan sayımı parametreleri, nötrofil lenfosit oranı, ortalama trombosit hacmi, preterm doğum, erken preterm doğum

ABSTRACT

Introduction: The complete blood count parameters and its combinations, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV), are inflammatory markers. In this study, we aimed to demonstrate the possible role of complete blood count parameters (NLR, PLR, and MPV) in predicting preterm birth.

Material and Methods: The complete blood count parameters in the first and third trimesters were recorded, as well as the corresponding NLR, PLR, and MPV. The study population was categorized as preterm (n = 94) and term births (n = 953). The preterm birth group was further divided into early preterm (n = 11) and late preterm birth (n = 83) groups. The inflammatory markers were compared between the study groups for the first and third trimesters separately. The alterations between the first and third trimester values were also compared.

Results: The first trimester values were similar across the study groups. Moreover, the MPV difference between the first and third trimesters was significantly lower in the preterm group than in the term group (0.0 ± 1.1 vs. 0.2 ± 1.1, p = 0.038). Furthermore, NLR values were higher in the early preterm subgroup than in the late preterm and term groups for the first and third trimesters (first trimester; 4.0 ± 1.2 vs. 3.1 ± 2.0 and 3.1 ± 1.3, p = 0.005; third trimester; 5.3 ± 1.2 vs. 4.0 ± 1.5 and 4.4 ± 2.9, p = 0.013).

Conclusion: NLR and MPV predict preterm births in the first trimester and before birth. This enables physicians to take some precautions in preventing preterm delivery.

Keywords: Complete blood count parameters, neutrophil to lymphocyte ratio, mean platelet volume, preterm delivery, early preterm birth

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INTRODUCTION

Defined as delivery before 37 weeks of gestation, preterm birth is one of the leading causes of neonatal mortality and morbidity and is an important complication of both singleton and multiple pregnancies worldwide (1). The incidence of preterm birth varies between 5%–13% among countries, and 15 million preterm births occur every year worldwide (2). Complications of preterm birth are estimated to be responsible for 35% of the 3.1 million annual neonatal deaths worldwide and are now the second most common cause of death in children under 5 years of age after pneumonia. In addition to causing mortality, preterm birth has lifelong effects on neurodevelopmental functions, leading to increased rates of cerebral palsy, learning difficulties, and visual impairments among newborns, as well as an increase in chronic diseases in adulthood (3). Preterm births are evaluated according to clinical causes and gestational week at the time of delivery. In 2013, the preterm birth rate in the USA was 11.4%, and the rate of births before 34 weeks was 3.4%. The risk of neonatal mortality and morbidity increased as the gestational week at delivery decreases (4). For these reasons, the prediction of preterm birth is important to reduce fetal mortality and morbidity and prevent unnecessary interventions.

The pathogenesis of preterm birth is not fully understood, but preterm birth can occur because of early idiopathic activation of the normal birth process or because of pathological processes. Pathological processes involved in preterm birth syndrome include intrauterine infection, uterine ischemia, uterine overstretching, abnormal allogeneic recognition, allergic-like reaction, cervical disease, and endocrine disorders (5). Among all suspected causes of preterm birth, infection and/or inflammation is the only pathologic process for which a solid causal relationship has been established, and whose molecular pathophysiology has been defined (6). One in four preterm infants is born to a mother with intra-amniotic infection, which is largely subclinical (7).

Various biomarkers related to inflammation have been examined as potential predictors of preterm birth (8). Complete blood count includes important parameters indicating inflammatory events. Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio have prognostic significance in diseases associated with systemic inflammation (9,10). Platelets are involved in the maintenance of hemostasis and thrombosis. However, there is a growing recognition that inflammation and immune response have a critical role (11). Mean platelet volume (MPV) is a measure of platelet size. MPV is a parameter indicating platelet function and activity (12). MPV disturbances reflect changes in the level of platelet stimulation or in the rate of platelet production. MPV has been used as a marker of platelet function in inflammatory diseases (13).

Prediction and prevention of preterm birth are recognized as a public health priority because of it's potential to reduce infant and childhood morbidity and mortality. Unfortunately, the progress in this regard has been limited. The present study investigated the role of complete blood count parameters and their changes in the first and third trimesters in predicting preterm birth.

MATERIALS AND METHODS

A retrospective observational study was conducted at Karabuk University Gynecology and Obstetrics Clinic between 2018 and 2020. The study was approved by the Local Ethics Committee of Karabuk University. We included women between the ages of 18 and 42, who had single pregnancies, were followed up at least once in the first and third trimesters, and whose pregnancy resulted in delivery. We excluded patients with pregestational or gestational conditions such as gestational hypertension, diabetes mellitus, hematological problems, thyroid disorders, hyperemesis gravidarum, active infection, threatened miscarriage, and those with a previous history of preterm birth which may complicate pregnancy and change the paramaters (14).

We reviewed the hospital database and collected data of 1047 patients who gave birth at 28 weeks and later. We recorded the maternal age, gravida, parity, the number of births, and body mass indices as baseline data for the patients. We equally examined the complete blood count parameters obtained in the first trimester and recorded the values of white blood cell, neutrophil, lymphocytes, platelet (PLT), red blood cell distribution width, platelet distribution width and MPV. Moreover, we recorded the same parameters in the complete blood count for women during the last trimester as routine follow-up at 1–2 weeks before delivery. We obtained the gestational age at birth, the type of delivery, birth weight of the newborn, and the first and fifth-minute APGAR(Activity-Pulse-Grimace-Appearance-Respiration) scores. The patients were divided into two groups: term (>37 gestational weeks) and preterm births (<37 gestational weeks). Additionally, patients with preterm birth were divided into two subgroups: early preterm birth (<34 gestational weeks) and late preterm birth (34–37 gestational weeks).

NLR and PLR values were calculated according to neutrophil, lymphocyte, and platelet values from complete blood counts. The NLR was obtained by dividing the absolute neutrophil count with the absolute lymphocyte count, while the PLR was calculated by dividing the platelet count with the absolute lymphocyte count. The differences between the third and first trimesters of the NLR, PLR, MPV, RDW, and PDW were also calculated and recorded.

We analyzed data using IBM SPSS Statistics version 21.0. The categorical variables, such as the type of birth, are presented as percentages. The quantitative variables were tested for normal distribution using the Shapiro–Wilk test. Normally distributed variables were analyzed using parametric tests such as T-test and ANOVA, while skewed-distributed variables were analyzed using the Mann–Whitney U and Kruskal–Wallis tests. A p value below 0.05 was considered statistically significant.

RESULTS

We examined 1047 patients, 953 of them had term births, and 94 delivered prematurely. Among this population, 637 underwent cesarean section, and 437 patients delivered pervaginally. While 22 (23%) of the preterm birth cases who had preterm labor did not receive any treatment due to preterm labor before delivery, 72 (77%) cases were hospitalized for preterm labor, received treatment (such as antenatal corticosteroids),

and were discharged during follow-up. They gave birth as preterm on their readmission later on. Delivery occurred before the 34th gestational week in 11 patients (11.7%) who had preterm delivery and between 34 and37 weeks in 83 patients (88.3%). Moreover, 410 patients (39.2%) delivered pervaginally, and 637 patients (60.8%) delivered by cesarean section.

We showed a comparison of the basal parameters and the hematological results detected in the first trimester between term and preterm deliveries in Table 1.

Table 1 Bazal and first trimester complete blood count parameters

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Gestational age at delivery (days)	272.3 ± 9.0	248.5 ± 9.8	<0.001
Age (years)	28.6 ± 5.5	28.8 ± 5.8	0.807
Gravida	2.2 ± 1.2	2.4 ± 1.3	0.286
Parity	2.0 ± 1.0	2.2 ± 1.1	0.157
Surviving	2.0 ± 1.0	2.2 ± 1.1	0.226
BMI (kg/m^2)	24.8 ± 5.7	25.6 ± 5.4	0.270
First Trimester; Complete blood count parameters			
WBC ($10^3/\mu L$)	8.6 ± 2.2	8.6 ± 2.1	0.758
NEU ($10^3/\mu L$)	5.9 ± 1.9	6.0 ± 1.9	0.717
Lym ($10^3/\mu L$)	2.1 ± 1.0	2.0 ± 0.6	0.621
PLT ($10^3/\mu L$)	254.0 ± 59.3	256.6 ± 55.7	0.765
MPV (f/L)	10.1 ± 1.2	10.1 ± 1.0	0.826
RDW (%)	14.1 ± 2.2	13.9 ± 1.3	0.719
PDW (%)	16.0 ± 0.6	16.0 ± 0.3	0.430
N/L ratio (NLR)	3.1 ± 1.3	3.3 ± 1.9	0.930
P/L ratio (PLR)	130.8 ± 39.3	135.9 ± 43.4	0.290

We could not detect significant differences between the groups. Although NLR and PLR values were higher in the preterm group, this difference was not significant. Table 2 shows the third trimester values and the differences between the third and first trimester data between the term and preterm birth groups. We found that the mean RDW values in the third trimester were significantly higher in cases with preterm delivery. Moreover, the difference between the third and first trimester values for MPV was lower in the preterm group. The first and third trimester values were similar, revealing possibly lower third trimester values. This shows that the low level of MPV could predict higher inflammation in the third trimester of the preterm group.

Table 2 Third trimester complete blood count parameters and the differences between these values among groups

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Third Trimester; Complete blood count parameters			
WBC ($10^3/\mu L$)	10.4 ± 2.5	10.3 ± 2.6	0.733
NEU ($10^3/\mu L$)	7.7 ± 2.2	7.7 ± 2.3	0.501
Lym ($10^3/\mu L$)	1.9 ± 0.8	2.0 ± 0.5	0.246
PLT ($10^3/\mu L$)	228.4 ± 62.7	233.6 ± 62.8	0.333
MPV (f/L)	10.2 ± 1.2	10.2 ± 1.3	0.603
RDW (%)	15.2 ± 3.0	14.6 ± 2.5	0.002
PDW (%)	16.4 ± 0.4	16.4 ± 0.4	0.617
N/L ratio (NLR)	4.4 ± 2.9	4.1 ± 1.4	0.321
P/L ratio (PLR)	127.0 ± 70.9	125.5 ± 51.5	0.751
Differences between third and first trimester complete blood count parameters			
N/L ratio (NLR)	1.3 ± 2.8	0.9 ± 2.0	0.536
P/L ratio (PLR)	-3.6 ± 70.6	-4.8 ± 51.5	0.973
MPV (f/L)	0.2 ± 1.1	0.0 ± 1.1	**0.038**
RDW (%)	1.0 ± 3.0	0.8 ± 2.4	0.098
PDW (%)	0.4 ± 0.6	0.3 ± 0.3	0.155

[a] p=0.004 [b] p=0.003 [c] p=0.004 [d] p=0.006

In Table 3, the early and late preterm groups were compared with the term group. The mean NLR value for first trimester was significantly higher in the <34-week group. Likewise, the third trimester NLR value was significantly higher in the <34-week group compared with the other groups.

Table 3 First and third trimester complete blood count paramteres and the differences between these values among subgroups

	>37 weeks (n=953)	34-37 weeks (n=83)	<34 weeks (n=11)	p
Gestational age at delivery (days)	272.5 ± 9.4	251.4 ± 4.9	225.7 ± 9.4	<0.001
First Trimester the complete blood count parameters				
N/L ratio (NLR)	3.1 ± 1.3 [a]	3.1 ± 2.0 [b]	4.0 ± 1.2[a, b]	**0.005**
P/L ratio (PLR)	130.8 ± 39.3	131.9 ± 46.3	158.9 ± 55.9	0.210
MPV (f/L)	10.1 ± 1.2	10.1 ± 1.0	10.0 ± 1.1	0.920
RDW (%)	14.1 ± 2.2	14.0 ± 1.2	13.9 ± 1.4	0.630
PDW (%)	16.0 ± 0.6	16.0 ± 0.3	16.0 ± 0.4	0.650
Third Trimester the complete blood count parameters				
N/L ratio (NLR)	4.4 ± 2.9 [c]	4.0 ± 1.5 [d]	5.3 ± 1.2 [c, d]	**0.013**
P/L ratio (PLR)	127.0 ± 70.9	126.7 ± 49.3	149.2 ± 91.5	0.774
MPV (f/L)	10.2 ± 1.2	10.2 ± 1.3	10.1 ± 1.6	0.547
RDW (%)	15.2 ± 3.0	14.9 ± 2.9	14.3 ± 1.4	0.143
PDW (%)	16.4 ± 0.4	16.4 ± 0.4	16.4 ± 0.3	0.790
Differences between third and first trimester complete blood count parameters				
N/L ratio (NLR)	1.3 ± 2.8	0.9 ± 2.0	1.3 ± 1.8	0.679
P/L ratio (PLR)	-3.6 ± 70.6	-5.1 ± 46.9	-9.7 ± 81.7	0.787
MPV (f/L)	0.2 ± 1.1	0.1 ± 1.1	0.1 ± 1.5	0.235
RDW (%)	1.0 ± 3.0	0.9 ± 2.5	0.3 ± 1.3	0.174
PDW (%)	0.4 ± 0.6	0.3 ± 0.3	0.4 ± 0.4	0.434

Although the differences in third and first trimester MPV values were similar between the groups, they were lower in preterm cases. Gestational age at birth, birth weights of the babies, and APGAR values were also compared between the study groups and are shown in Table 4. As we expected, the gestational age at birth, birth weights, and APGAR values were significantly higher in the group with term delivery.

Table 4 Delivery weeks and perinatal outcomes

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Gestational age at delivery (days)	272.3 ± 9.0	248.5 ± 9.8	<0.001
Newborn Weight	3316.1 ± 431.1	2734.4 ± 539.3	<0.001
APGAR 1 min.	8.8 ± 0.7	8.2 ± 1.2	<0.001
APGAR 5 min.	9.7 ± 0.6	9.4 ± 0.8	<0.001
C/S rate(%)	58.55	85.10	<0.001

DISCUSSION

In this study, the complete blood count parameters in the first and third trimesters in the preterm and term birth groups were similar. However, the difference in MPV between the first and third trimesters was significantly lower in the preterm delivery group compared with the term delivery group (p=0.038). When the preterm delivery group was further divided into early preterm and late preterm subgroups, the MPV differences were similar between the first and third trimesters (p=0.235). This finding demonstrates that the differences in MPV can predict preterm and term deliveries; however, it cannot discriminate early and late preterm deliveries. When NLR was considered in the first and third trimesters, although it was higher in the preterm delivery group, it was not significant. When the subgroups were analyzed, NLR values were significantly higher in the first and third trimesters of

the early preterm group (p=0.005 and p=0.013). However, the differences in NLR between the trimesters were not significant in any group. These findings suggest that a high NLR value in the first and third trimesters may predict possible preterm birth.

Preterm births are responsible for 75% of perinatal mortality and more than half of the long-term morbidity (15). Although preterm labor is currently accepted as a syndrome that can be initiated by infection or inflammation, uteroplacental hemorrhage, uterine overstretching, and different mechanisms; the only process whose molecular pathophysiology has been demonstrated is infection and/or inflammation (5,6).

Normal pregnancy relies on a fine balance between immune tolerance and suppression. It is known that tight regulation of maternal immune function in addition to its inflammatory components is crucial for a successful pregnancy, and that any imbalance between proinflammatory and anti-inflammatory cytokines and chemokines can lead to aberrant inflammation, often seen in complicated pregnancies such as preterm birth. Cytokines play a central role in preterm labor due to inflammation/infection (16). Inflammation is characterized by several basic processes, including exudation of plasma proteins, recruitment of leukocytes, and activation of cell- and plasma-derived inflammatory mediators (17). Infection and infection-induced activation of the inflammatory response are thought to be the leading risk factor for spontaneous preterm birth. As a result, increased production of proinflammatory cytokines is associated with uterine activation and preterm birth, whereas the production of anti-inflammatory cytokines plays an important role in the uterine quiescence during pregnancy (18).

Complete blood count is a simple, inexpensive, and readily available laboratory test in clinical practice. In pregnancy, it contains important parameters indicating inflammatory events in many pathological conditions. Especially, platelet and neutrophil counts elevate and lymphocyte counts decrease (19).

Neutrophils are the most abundant leukocytes in the peripheral blood. Neutrophils with antimicrobial effector mechanisms are deemed the central effectors of acute inflammation, forming the first line of defense of the innate immune response against most bacterial agents. Neutrophils are by far the most dominant leukocyte population in acute chorioamnionitis and in other infectious conditions associated with preterm birth (18). In addition to their role in the maintenance of pregnancy, the role of neutrophils in the induction of parturition remains controversial. Studies have shown that decidual neutrophils contribute to preterm birth by producing various inflammatory mediators and matrix metalloproteinases that promote rupture of fetal membranes (20). Recently, NLR has emerged as a new potential inflammatory biomarker and has been shown to be associated with adverse outcomes in obstetric complications, particularly in preeclampsia, gestational diabetes mellitus, and in different diseases (21,22). There are studies investigating the relationship between preterm birth and NLR in the literature. Akgün et al. showed that high NLR values may be associated with preterm births and newborns with low birth weight. They suggested that the maternal hyperinflammatory state accompanied by high NLR cause low birth weight and preterm birth by affecting the maternal placental fetal unit (14). Tolunay et al. also stated that high NLR may predict preterm delivery in pregnant women presenting with a threat of preterm birth (23). Similarly, in the study by Kurban et al., NLR was found to be higher in the preterm group compared with the term group, and when the preterm labor groups were divided into two subgroups as early and late, it was found that NLR was even higher in the early preterm group (24). We found that the NLR values of both the first and third trimesters were higher than in the early preterm groups. In a recent meta-analysis of 15 studies investigating the relationship between NLR and preterm birth, studies reported high and low levels of NLR. There is heterogeneity in the studies included in this meta-analysis due to differences in the gestational week at which blood samples were collected and in the definition of preterm labor. Nevertheless, the meta-analysis concluded that high NLR was associated with preterm birth (25). In our study, high NLR levels were found in both the first and third trimesters in the early preterm birth group. Therefore, high NLR levels in the first and last trimesters may be used as predictors of preterm birth.

While platelets are involved in the maintenance of hemostasis, many studies have shown that increased platelet count is associated with infection, inflammation, and malignancy (11,12,26). It has been reported that platelet activation increases after tissue damage and release of inflammatory mediators (12). MPV is a parameter indicating platelet function and activity (12). MPV is used as a marker of platelet function in inflammatory diseases. In inflammatory diseases, the number of circulating large platelets increases, and large numbers of large platelets migrate to sites of inflammation. The depletion of large platelets at the site of inflammation leads to an inverse relationship between MPV and platelet count. Cardio- and cerebrovascular disorders and low-grade inflammatory conditions prone to arterial and venous thrombosis are associated with high MPV, whereas low MPV levels are found in high-grade inflammatory diseases, such as active rheumatoid arthritis or familial Mediterranean fever attacks (27). In normal pregnancies, an increase in MPV is observed in the third trimester, but increased or decreased MPV levels have been reported in different pathologic conditions complicating pregnancy. In two different meta-analyses investigating MPV levels in preeclampsia and gestational diabetes mellitus, an increase in MPV was reported in both conditions (28,29). On the other hand, Ekin et al. found that low MPV level in the first trimester could be used as a more effective marker rather than platelet count in the prediction of preterm premature rupture of membranes (30). Similarly, in the study by Ersak et al. investigating platelet indices in placental abruption, low MPV levels were associated with a high degree of inflammation and accompanying platelet depletion (31). Because inflammation plays a critical role in the pathogenesis of preterm labor, changes in platelet function and thus in MPV are expected. In their study, Kurban et al. suggested that low MPV values predict preterm birth (24). In our study, no difference was observed between the first and third trimester MPV levels in the term and preterm birth groups; however, when the MPV change between the first and third trimesters was investigated, the increase in MPV was significantly lower in the preterm group. To our knowledge, this study is the first to evaluate MPV levels between the trimesters by taking serial complete blood count in the literature.

Because of the retrospective design of our study, there may be unidentified confounding variables that can affect the outcome of the study. Our study cohort consisted of women from a single hospital; therefore, it may be difficult to generalize our results to the entire female population. Additionally, the small number of patients in the preterm birth group may be considered a li-

mitation in terms of the study results. A strength of our study is that the sample size is larger than the studies in the literature. Another is that this is the first study in the literature that we know of in which the complete blood count in pregnant women is examined separately in the first and third trimesters, and the differences in these measurements are compared.

In conclusion, a complete blood count is a routine test for pregnancy, which is simple and cheap. To the best of our knowledge, this study is the first to evaluate the first and third trimester values of complete blood count parameters and its combinations, and the association between the differences in these parameters with preterm delivery. In our study, the increase in MPV between the first and third trimesters was significantly lower in the preterm group, and NLR was higher in both the first and third trimesters in the early preterm group. We think that NLR value in the first and third trimesters and MPV changes between trimesters can be used in the prediction of preterm birth due to inflammatory processes. Further studies are needed to validate these findings in clinical practice.

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Erken Evre Serviks Kanserinde (FIGO 2014 Evre IB1–IIA2) Uterin İnvazyonu Öngören Faktörler

Predicting factors of uterine invasion in early-stage (FIGO 2014 Stage IB1–IIA2) cervical cancer

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ÖZ

Amaç: Uterin korpus tutulumu daha önceki çalışmalarda radyolojik olarak gösterilmiş veya endometriyal biyopsi ile teşhis edilmiştir. Bu nedenle, radikal histerektomi örneklerinde uterin korpus tutulumunu saptayan az sayıda çalışma vardır. Bu çalışma, cerrahi olarak tedavi edilen serviks kanseri hastalarında uterin korpus tutulumunu etkileyen faktörleri araştırmak için tasarlanmıştır.

Materyal ve Metot: Ocak 2008-Ağustos 2021 tarihleri arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi ve Ankara Bilkent Şehir Hastanesinde radikal histerektomi ve pelvik-paraaortik lenfadenektomi yapılan klinik erken evre (evreIB1-IIA2) serviks kanserli toplam 269 hasta çalışmaya alındı ve klinikopatolojik verileri hasta dosyalarından veya hastanenin elektronik veri tabanından çıkarıldı.

Bulgular: Uterin invazyon 102 (%37.9) hastada pozitifti. Hastaların tümör boyutu 66 (%24,5) hastada ≤20 mm, 82 (%30,5) hastada >40 mm idi. 44 (%16.4) hastada parametrial invazyon saptandı. Multivariant analizde; tümör tipi (adenokanser ve diğer tümör tipleri) (HR: 8,94; %95 GA: 3,569–22,401; p<0,001), tümör boyutu (>35 mm-≤35 mm) (HR: 2,34; %95 GA: 1,234) –4,440; p=0,009) stromal invazyon derinliği (>1/2 vs. ≤1/2) (HR: 6,63; %95 GA: 2,205–19,952; p<0,001), parametrial metastaz (pozitif vs. negatif) (HR: 2,86; %95 GA: 1,220–6,707; p=0,016) uterin invazyonun bağımsız belirleyicisi olarak bulundu.

Sonuç: Tümör tipi, stromal invazyon derinliği ve parametrial metastaz, uterin korpus invazyonu için bağımsız risk faktörleriydi. Serviks kanseri evrelemesini belirlemede geleneksel olarak cerrahi-patolojik bulgular kullanılmamasına rağmen serviks kanserinin tedavisinde uterin invazyonun varlığının önemli bir rol oynayacağına inanıyoruz.

Anahtar Kelimeler: Serviks kanseri, uterin invazyon, radikal histerektomi

ABSTRACT

Objective: Uterine corpus involvement was demonstrated radiologically or diagnosed by endometrial biopsy in the previous reports. Thus, there are few studies that detect uterine corpus involvement in radical hysterectomy specimens. This study was designed to investigate the factors that influence uterine corpus involvement in surgically treated cervical cancer patients.

Materials and Methods: A total of 269 patients with clinical early-stage (stageIB1-IIA2) cervical cancer who underwent radical hysterectomy and pelvic-paraaortic lymphadenectomy at Zekai Tahir Burak Women's Health Training and Research Hospital and Ankara Bilkent City Hospital between January 2008 and August 2021 were recruited, and their clinicopathologic data were extracted from their patient files or the hospital's electronic database.

Results: Uterine invasion was positive in 102 (37.9%) patients. Tumor size of patients was ≤20 mm in 66 (24.5%) patients and >40 mm in 82 (30.5%). Parametrial invasion was detected in 44 (16.4%) patients. In the multivariate analysis; tumor type (adenocancer vs. other tumor types) (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size (>35 mm vs. ≤35 mm) (HR: 2.34; 95% CI: 1.234–4.440; p=0.009) depth of stromal invasion (>1/2 vs. ≤1/2) (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), parametrial metastasis (positive vs. negative) (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were found to be independent predictor of uterine invasion.

Conclusion: Tumor type, stromal invasion depth, and parametrial metastasis were independent risk factors for invasion of the uterine corpus. We believe that the presence of uterine invasion will play an important role in the treatment of cervical cancer, despite the fact that surgical-pathologic findings have not traditionally been used to determine cervical cancer staging.

Keywords: Cervical cancer, uterine invasion, radical hysterectomy

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INTRODUCTION

Cervical cancer was the fourth most prevalent cancer in women in 2020 GLOBOCAN, with an estimated 604,000 new cases and 342,000 deaths globally. (1, 2). Traditionally, cervix cancer was staged clinically; however, surgical and radiologic evaluation are now included in the staging criteria. (3-6). Surgical and radiologic staging provides crucial information that can influence treatment. (7). Direct tumor invasion, lateral invasion into the parametria, distant invasion into the upper vagina, and, much less frequently, anterior-posterior invasion into the bladder or rectum are the most common ways that cervical cancer spreads. (8). In the current staging system for cervical cancer, these anatomical sites of direct tumor extension are considered, and the presence of tumor invasion in these anatomical sites is associated with a poorer prognosis. (9). In the 2018 International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging system, imaging and pathologic findings could be used to determine the stage of the disease. (4). Uterine corpus involvement, on the other hand, has been disregarded in this new model, just as it has been in previous FIGO staging systems. Involvement of adjacent anatomic structures, other than the uterine corpus, is associated with a poor prognosis and changes the FIGO stage, according to the most recent FIGO staging system. (4). Patients with early-stage cervical cancer who underwent radical hysterectomy were found to have uterine corpus invasion at a rate ranging from 4.9% to 26.2%, according to the pathology specimens of several studies. (10-16). Furthermore, previous studies had linked uterine corpus involvement to poorer oncologic outcomes in patients with cervical cancer.(10, 16).

In prior reports, involvement of the uterine corpus was demonstrated radiologically or diagnosed via endometrial biopsy. Thus, studies detecting uterine corpus involvement in radical hysterectomy specimens are limited (12, 17). Therefore, we designed this study to investigate the factors that influence uterine corpus involvement in surgically treated cervical cancer patients.

MATERIALS AND METHODS

A total of 269 patients with clinical early-stage (stageIB1-IIA2) cervical cancer who underwent radical hysterectomy and pelvic-paraaortic lymphadenectomy at Zekai Tahir Burak Women's Health Training and Research Hospital and Ankara Bilkent City Hospital between January 2008 and August 2021 were recruited, and their clinicopathologic data were extracted from their patient files or the hospital's electronic database. Before beginning the study, approval from the institutional review board was obtained. Gynecologic oncologists performed all surgical procedures. A type III radical hysterectomy was carried out, during which the uterus, the cervix, the upper third of the vagina, and the parametrial resection up until the pelvic sidewall were all removed. It was decided to perform a bilateral salpingo-oophorectomy on the patient after evaluating their age and the general appearance of their ovaries. A radical hysterectomy, pelvic lymph node dissection, and paraaortic lymph node dissection consist the standard surgical protocol for cervical cancer. Lymphadenectomy involved dissecting pelvic and paraaortic lymph nodes to the inferior mesenteric artery or left renal vein. All surgical specimens were evaluated by specialized gynecologic pathologists. Before opening the radical hysterectomy specimen to expose the cervix and endometrium for a macroscopic examination of the cervical cancer, the specimen was externally examined. The location, growth pattern, size, and extent of the tumor's spread were all recorded. Deep stromal invasion was defined as tumor invasion of the outer half of the cervical stroma (>1/2 of full thickness). It was determined that lymphovascular space invasion (LVSI) was present when epithelial tumor cells were found in the lumen of vessels, which were lined by endothelial cells. Surgical margin involvement was defined as tumor positivity within a 5-mm margin of the pathology specimen. Vaginal involvement refers to the presence of a tumor elsewhere within the vaginal region. Cervical tumors were categorized into 4 types: squamous cell cancer, adenocancer, adenosquamous and others. Uterine invasion was defined as endometrial and/or myometrial disease that had spread above the internal cervical ostium. For staging, FIGO 2014 criteria are utilized.

The Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL) version 20.0 was utilized for data recording and statistical analysis. The Kolmogorov–Smirnov test was used to assess the normality of continuous variable distributions. The analysis of categorical variables was conducted using either Pearson's Chi-square ($\chi 2$) test or Fisher's exact test, depending on which method was deemed more appropriate for the circumstances. The difference between samples from non-normal distributions was analyzed using the Mann-Whitney-U test. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on uterine invasion. Variables that were statistically significant in univariate analysis were incorporated into a model for multivariate analysis.

RESULTS

A total of 269 patients with a mean age of 51.8 years (range, 26–80 years) were analyzed. The mean tumor size of the patients was 35.8 mm (range, 5–130 mm). The mean number of removed lymph nodes was 56.4 (range, 8–140). The mean number of metastatic lymph node was 6.5 (range, 1–73).

Tumor type of patients was squamous cell carcinoma in 190 (70.6%) patients, adenocarcinoma in 48 (17.8%), adenosquamous cell carcinoma in 25 (9.3%) and other in 6 (2.2%). Patients FIGO 2014 stage was IB1 in 148 (55%) patients, IB2 in 57 (21.2%), IIA1 in 38 (14.1%) and IIA2 in 26 (9.7%). Uterine invasion was positive in 102 (37.9%) patients. Tumor size of patients was ≤20 mm in 66 (24.5%) patients and >40 mm in 82 (30.5%). Parametrial invasion was detected in 44 (16.4%) patients. Surgical border involvement was positive in 22 (8.2%) of the patients. Vaginal invasion was positive in 68 (25.3%) of the patients. LVSI was positive in 197 (73.2%) patients. Deep stromal invasion was detected in 209 (77.7%) patients. Bilateral salpingo-oophorectomy was performed in 256 (95.2%) patients. Ovarian metastasis was positive in 15 (5.6%) patients. Lymph node metastasis was positive in 98 (36.4%) patients (Table 1).

Table 1. Clinical Features

Features		**Mean±SD**	**Median (Range)**
Age at initial diagnosis		51.8±11.5	52 (26-80)
Tumor size (mm)		35.8±17.4	35 (5-130)
Number of removed lymph nodes		56.4±23.1	53 (8-140)
Number of metastatic lymph node		6.5±12.2	2 (1-73)
		n	**Percentage**
Tumor type	Squamous cell carcinoma	190	70.6
	Adenocarcinoma	48	17.8
	Adenosquamous cell carcinoma	25	9.3
	Other [1]	6	2.2
FIGO 2014 stage	IB1	148	55
	IB2	57	21.2
	IIA1	38	14.1
	IIA2	26	9.7
Tumor size	≤20 mm	66	24.5
	>20 mm - ≤40 mm	121	45
	>40 mm	82	30.5
Parametrial invasion	Negative	225	83.6
	Positive	44	46.4
Surgical border involvement	Negative	247	91.8
	Positive	22	8.2
Vaginal invasion	Negative	201	74.7
	Positive	68	25.3
Lymphovascular space invasion	Negative	72	26.8
	Positive	197	73.2
Stromal invasion	≤%50	60	22.3
	>%50	209	77.7
Bilateral salpingo-oophorectomy	Not performed	13	4.8
	Performed	256	95.2
Ovarian metastasis	Negative	241	94.1
	Positive	15	5.6
Uterine invasion	Negative	167	62.1
	Positive	102	37.9
Lymph node metastasis	Negative	171	63.6
	Positive	98	36.4
Site of metastatic lymph node	Only pelvic	80	81.6
	Only paraaortic	-	-
	Pelvic and paraaortic	18	18.4

[1]: Neuroendocrine (n:3), lymphoepithelioma (n:2), basoloid (n:1) Clinic, surgical and pathologic factors predicting uterine invasion is shown in table 2. Histopathology, tumor size, FIGO 2014 stage, LVSI, vaginal involvement, deep stromal invasion, parametrial invasion, and ovarian metastasis were statistically significant ($p<0.05$) for uterine invasion in univariate analysis.

Clinic, surgical and pathologic factors predicting uterine invasion is shown in table 2. Histopathology, tumor size, FIGO 2014 stage, LVSI, vaginal involvement, deep stromal invasion, parametrial invasion, and ovarian metastasis were statistically significant (p<0.05) for uterine invasion in univariate analysis.

Table 2. Clinic, surgical and pathologic factors predicting uterine invasion

Factors		**Uterine Invasion**				***P* Value**
	Negative		**Positive**			
	n	**%**	**n**	**%**		
Age at initial diagnosis [1]	≤52 years	96	65.3	51	34.7	*0.254*
	>52 years	69	58.5	49	41.5	
Histopathology	Squamous cell carcinoma	133	70	57	30	***<0.001***
	Adenocancer	17	35.4	31	64.6	
	Adenosquamous	14	56	11	44	
	Other type	3	50	3	50	
Tumor size	≤20 mm	57	86.4	9	13.6	***<0.001***
	>20 mm - ≤40 mm	71	58.7	50	41.3	
	>40 mm	39	47.6	43	52.4	
Tumor size [1]	≤35 mm	107	74.8	36	25.2	***<0.001***
	>35 mm	60	47.6	66	52.4	
FIGO 2014 stage	IB1	109	73.6	39	26.4	***<0.001***
	IB2	28	49.1	29	50.9	
	IIA1	19	50	19	50	
	IIA2	11	42.3	15	57.7	
FIGO 2014 stage	I	137	66.8	68	33.2	***0.004***
	II	30	46.9	34	53.1	
Lymphovascular space invasion	Negative	53	73.6	19	26.4	***0.018***
	Positive	114	57.9	83	42.1	
Surgical border involvement	Negative	157	63.6	90	36.4	*0.093*
	Positive	10	45.5	12	54.5	
Vaginal involvement	Negative	136	67.7	65	32.3	***0.001***
	Positive	31	45.6	37	54.4	
Stromal invasion	≤%50	57	91.9	5	8.1	***<0.001***
	>%50	110	53.1	97	46.9	
Parametrial invasion	Negative	153	68	72	32	***<0.001***
	Positive	14	31.8	30	68.2	
Lymph node metastasis [2]	Negative	116	67.8	55	32.2	***0.010***
	Positive	51	52	47	48	
Ovarian metastasis	Negative	153	63.5	88	36.5	***<0.001***
	Positive	2	13.3	13	86.7	

[1] **Other tumor types:** Squamous cell cancer + Adenosquamous cell carcinoma + Neuroendocrine + Lymphoepithelioma + Basoloid

In the multivariate analysis; tumor type (adenocancer vs. other tumor types) (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size (>35 mm vs. ≤35 mm) (HR: 2.34; 95% CI: 1.234–4.440; p=0.009) depth of stromal invasion (>1/2 vs. ≤1/2) (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), parametrial metastasis (positive vs. negative) (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were found to be independent predictor of uterine invasion (Table 3).

Table 3. Multivariate Analysis

Factors	Hazard Ratio	95% Confidence Interval
Tumor type (a*denocancer vs. other tumor types* [1])	8.941	3.569-22.401
Tumor size (*>35 mm vs. ≤35 mm*)	2.340	1.234-4.440
FIGO stage (*II vs. I*)	2.698	0.227-32.032
Lymphovascular invasion (*positive vs. negative*)	1.247	0.591-2.633
Vaginal spread (*positive vs. negative*)	3.766	0.329-43.054
Depth of stromal invasion (*>1/2 vs. ≤1/2*)	6.633	2.205-19.952
Lymph node metastasis (*positive vs. negative*)	1.093	0.564-2.118
Ovarian metastasis (*positive vs. negative*)	3.679	0.698-19.396
Parametrial metastasis (*positive vs. negative*)	2.861	1.220-6.707

DISCUSSION

Cervical cancer spreads primarily through direct extension and lymphatic dissemination. In our study of early-stage cervical cancer patients treated with radical hysterectomy, uterine invasion was detected in 37.9% of patients. The remarkable findings of the present study were that tumor type (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size >35 mm (HR: 2.34; 95% CI: 1.234–4.440; p=0.009), depth of stromal invasion (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), and parametrial metastasis (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were independent predictors of uterine invasion.

Kim et al. investigated the relationships between FIGO stage, tumor volume, and uterine body invasion in a study of 106 patients with IB-IIIB cervical carcinoma. (18). Patients with FIGO stage I had a uterine invasion rate of 33.3%, patients with FIGO stage II had a 63.3% rate, and patients with FIGO stage III had an 83.3% rate. There was a significant correlation between FIGO stage and uterine invasion rate (p = 0.007). Uterine invasion was observed in 44.3% of patients with a small tumor volume (30 ml; n=27) and in 86.7% of patients with a large tumor volume (30 ml; n=39); and was strongly correlated with tumor volume as measured by magnetic resonance imaging. (18).

Weili et al. included 2212 patients in their study; 515 patients with cervical cancer had uterine corpus invasion and 1.697 patients with cervical cancer had no uterine corpus invasion (19). In this study, patients with uterine corpus invasion were significantly older, had significantly larger tumors, and were significantly more likely to have advanced stage disease, adenocarcinoma, grade 1 or 2 disease, stromal invasion depth >1/2, parametrial involvement, resection margin involvement, and lymph node metastasis than those without uterine corpus invasion. (19). Similar to Weili et al., tumor size, histopathology, FIGO 2014 stage, stromal invasion, parametrial invasion, and LVSI were statistically significant in predicting uterine invasion in our study in univariate analysis.

Turan et al. included 354 patients in their study; uterine invasion was detected in 60 (16.9%) patients (20). They found that the presence of uterine invasion was significantly associated with the histologic subtype of the tumor (adenocarcinoma, adenosquamous), the size of the primary tumor (≥20 mm), the presence of LVSI, surgical margin involvement, vaginal involvement, deep stromal invasion, parametrial invasion, and the presence of lymph node metastasis. (20).

Matsuo et al. found that non-squamous histology, which includes adenocarcinoma, is an independent risk factor for uterine corpus tumor invasion in comparison to squamous type. (16). While this finding may partially support the hypothesis that squamous type and adenocarcinoma type have different patterns of tumor spread, with lymphatic spread being more prevalent in squamous histology and hematogenous spread being more common in adenocarcinoma histology, the most likely cause of this association is the anatomical proximity to the uterine corpus. Because the endocervix is anatomically closer to the uterine corpus than the extocervix, there is a greater likelihood of direct extension of adenocarcinoma to the uterine corpus. (16). Similar to Matsuo et al. in our study, adenocarcinoma was the most common (%64.6) histopathology in cervical cancer patients with uterine invasion. Moreover, in this study, Matsuo et al. emphasized that, on multivariate analysis, uterine corpus tumor invasion was independently associated with older age, non-squamous histology, high-grade tumors, and large tumor size (16).

He et al. retrospectively reviewed 1414 patients with stage IA2–IIB cervical cancer from 11 medical institutions in China who underwent radical hysterectomy between 2004 and 2016.They indicated that a myometrial invasion ≥50% within the uterine corpus was an independent factor associated with a poorer prognosis in patients who had cervical cancer. On the other hand, endometrial invasion and myometrial invasion <50% had no effect on the patients' outcomes. Furthermore Turan et al. found that in their study cohort, the 5-year cancer-specific survival rate was 94%. Uterine invasion and lymph node metastasis were identified as independent risk factors for cancer-specific survival (20).

The most important limitation of this study is its retrospective design. Furthermore, there is a lack of preoperative evaluation data for uterine invasion. The inclusion of a moderately large number of patients who underwent radical hysterectomy performed by gynecologic oncologists and the identification of uterine

invasion in pathology specimens by gynecologic pathologists were the study's major strengths.

In conclusion, tumor type, depth of stromal invasion and parametrial metastasis were independent risk factors for uterine corpus invasion. Even though cervical cancer staging has not traditionally been based on surgical-pathologic findings, we believe that the presence of uterine invasion will be important in the treatment. More large-scale prospective studies are needed to determine the significance of uterine invasion in cervical cancer.

Conflict of Interest

None. The manuscript has been read and approved for submission by all the named authors.

Author Contribution

Abdurrahman Alp Tokalioglu conceived and designed the study and wrote the manuscript. Fatih Celik, Okan Aytekin and Burak Ersak collected clinical data. Ilker Selcuk and Izzet Ozgurluk analyzed the histological data. Abdurrahman Alp Tokalioglu wrote, and edited the manuscript. Ozlem Moraloglu Tekin and Bulent Ozdal reviewed the manuscript. All authors participated in interpretation of the results and writing of the report and approved the final version submitted.

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Neuroprotective antenatal magnesium therapy and immediate neonatal outcomes : a case control study

Nöroprotektif antenatal magnezyum tedavisinin prematürelerde erken dönem sonuçları: vaka-kontrol çalışması

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ÖZ

Amaç: Antenatal magnezyum sülfat uygulamasının uzun dönemde nöroprotektif etkisi kanıtlansa da pretermlerde doğum sonrası erken dönem yan etkilerine dair yapılan çalışma sonuçları çelişkilidir. Bu çalışmada nöroprotektif amaçlı antenatal magnezyum sülfat tedavisinin prematüre bebeklerde erken dönemde kardiyopulmoner fonksiyonlar ve serum elektrolitleri üzerine etkisi araştırılmıştır.

Gereçler ve Yöntem: Ocak 2017- Aralık 2018 yılları arasında ≤ 32 gestasyon haftası doğan, ünitemizde takip edilen ve postnatal ilk 48 saati içinde serum magnezyum düzeyi alınan yenidoğanlar dahil edildi. Major konjenital malformasyonu, kromozom anomalisi olanlar, dosya bilgileri eksik olanlar dışlandı. Preeklampsi ve eklampsi için magnezyum sülfat anne bebekleri çalışmaya dahil edilmedi. Erken doğum riski nedeniyle antenatal dönemde nöroprotektif amaçla magnezyum sülfat tedavisi uygulanan anne bebekleri vaka grubunu oluşturdu. Gestasyon haftasına göre bire bir eşleştirme yapılarak kontrol grubu belirlendi. Hasta dosyalarından demografik veriler, doğum salonunda resüsitasyon ihtiyacı, sürfaktan ihtiyacı, ilk gün solunum desteği, kalp tepe atımı (KTA), kan basıncı ,ilk 48 saatte elektrolit değerleri, tam enteral beslenme süresi, eşlik eden major morbiditeler ve erken dönem mortalite kayıt edildi.

Bulgular: Toplamda 156 hasta çalışmaya dahil edildi. Nöroprotektif amaçlı antenatal magnezyum alan 78 prematüre, antenatal magnezyum almayan 78 kontrol ile karşılaştırıldı. Gestasyon yaşları ve doğum ağırlıkları (sırasıyla 28.3(±1.8) hafta ve 28.4 (±2.4) hafta; 1113 (±301) gr ve 1160 (±329) gr benzerdi (p=0,41, p=0,54)). Anne magnezyum düzeyi ve bebek ilk magnezyum düzeyi , antenatal magnezyum alan grupta daha yüksekti. Doğumda entübasyon ihtiyacı, hipotansiyon varlığı, ilk 24 saat mekanik ventilasyon desteği, ilk 24 saat oksijen ihtiyacı ve mortalite oranı arasında iki grup arasında anlamlı fark yoktu. Antenatal magnezyum alan grupta ilk 24 saat ortalama KTA daha düşüktü ancak ortalama >120/dk idi.

Sonuç: Nöroprotektif amaçlı antenatal magnezyum sülfat kullanımı prematüre bebekte postnatal erken dönemde güvenilirdir

Anahtar kelimeler: prematüre, magnezyum sülfat, nöroprotektif

ABSTRACT

Aim: Antenatal magnesium sulfate administration has been shown to have a long-term neuroprotective effect, but its immediate impact on preterm infants' immediate neonatal outcomes remains subject of controversy. In this study, we aimed to investigate the effect of antenatal magnesium sulfate treatment on early cardiopulmonary functions and serum electrolytes in preterm infants born ≤32 gestational weeks.

Material-Methods: We included preterm infants born ≤32 gestational weeks who were followed up in our unit and had their serum magnesium levels obtained within the first 48 hours postnatally. Infants with major congenital malformations, chromosomal abnormalities, and missing data were excluded. Infants born to mothers who received magnesium sulfate for preeclampsia or eclampsia were also excluded. The case group consisted of preterm infants born to mothers who received magnesium sulfate treatment for neuroprotection in the antenatal period due to the risk of preterm delivery, while the control group was matched one-to-one according to gestational week. We recorded demographic data including; need for resuscitation in the delivery room, need for surfactant, respiratory support on the first postnatal day, mean heart rate, mean blood pressure, and electrolyte values in the first 48 hours, as well as major morbidities and early mortality from patient files.

Results: A total of 156 patients were included in the study, with 78 premature infants receiving magnesium sulfate for neuroprotection and 78 controls who did not. Gestational ages and birth weights were similar between the two groups. Maternal magnesium level and infant initial magnesium level were higher in the group receiving antenatal magnesium. The need for intubation at birth, presence of hypotension, mechanical ventilation support for the first 24 hours, the mean oxygen requirement for the first 24 hours, and mortality rate were not significantly different between the two groups. In the case group, the mean heart rate for the first 24 hours was lower but still >120/min.

Conclusion: Our study findings suggest that antenatal use of magnesium sulfate for neuroprotection is safe in the early postnatal period in premature infants.

Keywords: prematurity, magnesium sulphate, neuroprotection

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GİRİŞ

Preterm doğum serebral palsi için en önemli risk faktörlerinden biridir ve uzun dönemde nörokognitif bozukluk riski gestasyonel hafta düştükçe belirgin şekilde artmaktadır (1). Daha önce yapılan üç meta-analizde antenatal magnezyum sülfat (MgSO4) uygulamasının pretermlerde uzun dönemde serebral palsi ve kaba motor disfonksiyon riskini azalttığı gösterilmiştir. Bu nedenle Amerikan Jinekoloji ve Obstetri Derneği 2010 yılından itibaren rehberlerinde acil preterm doğum riski olan gebelere fetal nöroprotektif amaçlı antenatal MgSO4 verilmesini önermektedir (2-5).

İntrapartum MgSO4 uygulaması sonrası maternal serum magnezyumun plasenta aracılığıyla direk fetusa geçişi nedeniyle antenatal hipermagnezemi durumunda doğum sonrası preterm bebeklerde ilk günlerde geçici hipermagnezemi görüldüğü bilinmektedir (2). Yapılan bir çalışma anne ve bebek serum magnezyum düzeylerinin yüksek oranda korelasyonunu göstermiştir (6). Bunun yanında daha önce yapılan çalışmalar geçici hipermagnezeminin preterm bebeklerde erken dönemde hipotansiyon, solunum depresyonu, intraventriküler kanama, beslenme intoleransı ve kalp yetmezliği riskini artırabileceğini göstermiştir (6-9). Ayrıca antenatal MgSO4 tedavisine ikincil prematür bebekte semptomatik erken başlangıçlı hiperkalemi gelişimini bildiren vakalar da vardır (10) .

Bu nedenle bu retrospektif vaka–kontrol çalışmasının amacı antenatal MgSO4 tedavisinin prematüre bebeklerde erken dönemde kardiyopulmoner fonksiyonlar ve serum elektrolitleri üzerine etkisini araştırmaktır.

MATERYAL-METOD

Çalışma tek merkezli retrospektif vaka–kontrol çalışması olarak dizayn edildi. Ankara Dr. Zekai Tahir Burak Eğitim Kadın Sağlığı Eğitim Ve Araştırma Hastanesi, üçüncü basamak yenidoğan yoğun bakım ünitesinde (YYBÜ) Ocak 2017 ve Aralık 2018 tarihleri arasında takip edilen hastaların verileri kullanıldı. Çalışma için Sağlık Bilimleri Üniversitesi Ankara Bilkent Şehir Hastanesi Etik Kurulu'ndan onay alınmıştır (protokol no: E2-21-513). Çalışmaya hastanemizde ≤ 32 gestasyon haftası doğan ve postnatal ilk dört hafta ünitemizde takip edilen, doğum öncesi anneden serum magnezyum düzeyi gönderilen, postnatal ilk 48 saati içinde serum magnezyum düzeyi alınan yenidoğanlar dahil edildi. Major konjenital malformasyonu, kromozom anomalisi olanlar ve doğum sonrası takip verilerinde eksiklik olan hastalar çalışmadan çıkartıldı. Maternal preeklampsi ve eklampsi nedeniyle magnezyum sülfat uygulanan anne bebekleri çalışmaya dahil edilmedi. Erken doğum riski nedeniyle antenatal dönemde nöroprotektif amaçla MgSO4 tedavisi uygulanan anne bebekleri vaka grubunu oluşturdu. Toplamda 78 hasta vaka grubunu oluşturdu. Gestasyon haftasına göre bire bir eşleştirme yapılarak kontrol grubu belirlendi. Çalışmaya toplamda 156 hasta dahil edildi.

Erken doğum tehdidi olan, ≤32 gestasyon haftasındaki gebelere magnezyum sülfat; ilk 30 dakikada intravenöz olarak 4 gr yükleme dozundan uygulandı takipte en az 12 saat boyunca ya da doğuma kadar olacak şekilde 1-2 gr /saat dozundan idame tedavisi olarak verildi. Hastaların bazal demografik ve klinik özellikleri; gebelik haftası, doğum ağırlığı, cinsiyeti, antenatal steroid ihtiyacı, 1 ve 5. dk APGAR skoru, doğum salonunda resüsitasyon öyküsü, surfaktan ihtiyacı, ilk beslenmeye başlangıç günü, tam enteral beslenme günü kayıt edildi. Neonatal morbiditeler: erken neonatal sepsis (ENS) (postnatal ilk 3 gün içinde kanıtlanmış sepsis) , patent duktus arteriyozus (PDA) (medikal veya cerrahi tedavi gerektiren), nekrozitan enterokolit (NEK) (≥evre 2) , tedavi gerektiren prematüre retinopatisi (ROP), intraventriküler kanama (İVK) (≥evre 3) , periventriküler lökomalazi (PVL), hastanede yatış süresi ve mortalite bilgileri yatış dosyasından değerlendirildi (10-14). Ayrıca ilk 24 saatte; mekanik ventilasyon ihtiyacı, ortalama Fio2 ihtiyacı, ortalama kalp hızı, tedavi gerektiren hipotansiyon varlığı ve postnatal ilk 48 saatte bakılan sodyum, potasyum, kalsiyum ve magnezyum düzeyi kayıt edildi. Annenin yaşı, koryoamniyonit öyküsü, erken membran rüptürü öyküsü ve serum magnezyum, kalsiyum, potasyum düzeyi anne dosyasından not edildi.

İstatistik

İstatistiksel analizler, SPSS (Statistical Package for the Social Sciences) 23.0 İstatistiksel paket programı kullanılarak değerlendirildi. Sürekli değişkenler ortalama±standart sapma ve ortanca (minimum- maksimum) olarak verildi. Kategorik değişkenler sıklık ve yüzdeler ile ifade edildi. Verilerin normal dağılıma uygunlukları Shapiro-Wilk normallik testi ile değerlendirildi. Parametrik veriler; Student's t-testi ve paired t-testi ile, parametrik olmayan veriler; ki-kare testi ve Mann- Whitney U testi ile analiz edildi. Tüm istatiksel analizler için p<0.05 anlamlı olarak kabul edildi.

BULGULAR

Toplamda 156 hasta çalışmaya dahil edildi. Nöroprotektif amaçlı antenatal MgSO4 alan 78 prematüre, gestasyon haftasına göre 1'e 1 eşleştirilmiş olarak antenatal MgSO4 almayan 78 kontrol ile karşılaştırıldı. Tablo 1'de çalışma gruplarının klinik ve demografik özellikleri özetlendi. Gestasyon yaşları ve doğum ağırlıkları (sırasıyla 28.3(±1.8) hafta ve 28.4 (±2.4) hafta; 1113 (±301) gr ve 1160 (±329) gr benzerdi (p=0,41, p=0,54)). MgSO4 alan grupta antenatal steroid uygulanma oranı daha yüksekti (p<0.01) (Tablo 1).

Tablo 1. Çalışma gruplarının klinik ve demografik özelliklerinin karşılaştırılması

	Antenatal magnezyum kullanımı		*p value*
	Vaka (n=78)	Kontrol (n=78)	
Gestasyonel yaş, hafta*	28.3 ±1.8	28.4± 2.4	0.41
Doğum ağırlığı, gr *	1113 ± 301	1160 ± 329	0.54
Erkek cinsiyet, *s (%)*	48 (61.5)	44 (56.4)	0.36
1.dakika Apgar skoru †	5 (1-7)	5 (1-8)	0.84
5. dakika Apgar skoru	7 (2-9)	8 (3-9)	0.38
Sezeryan, *s (%)*	69 (88.4)	59 (75.6)	0.06
Doğumda entübasyon, *s (%)*	30 (38.4)	28 (32)	0.59
Antenatal steroid kullanımı, s *(%)*	74 (94.8)	55 (70.5)	<0.01
RDS, s *(%)*	40 (51.3)	42 (53.8)	0.85
ENS, s *(%)*	5 (6.2)	6 (7.7)	0.19
Tam enteral beslenme, gün *	16.2 ± 6·4	16.8± 7·2	0.42
İVK/PVL, *s (%)*	13 (16.6)	12 (15.4)	0.41
ROP, *s (%)*	6(7.6)	7(8.9)	0.86
PDA, *s (%)*	21(26.9)	28 (35.9)	0.34
NEK, *s (%)*	9 (11.5)	6 (7.7)	0.52
Mortalite, *s (%)*	16 (20.5)	12 (15.4)	0.35
Anneye bağlı özellikler			
Koryoamniyonit, *s (%)*	10 (12.8)	11 (14.1)	0.63
Erken membran rüptürü, *s (%)*	13 (16.6)	13 (16.6)	1

p<0.05 anlamlı kabul edildi

*Ortalama ± Standart sapma, †Ortanca (minimum-maksimum) RDS: respiratuar distress sendromu, ENS: erken neonatal sepsis, İVK: intraventriküler kanama, PVL: periventriküler lökomalazi, ROP: prematüre retinopatisi, NEK: nekrozitan enterokolit

Anne serum magnezyum düzeyi ve bebek ilk serum magnezyum düzeyi antenatal MgSO4 alan grupta daha yüksekti ancak diğer elektrolit düzeyleri arasında istatistiksel olarak belirgin fark yoktu. Doğumda entübasyon ihtiyacı (p=0.59), hipotansiyon varlığı (p=0.22), ilk 24 saat mekanik ventilasyon desteği (p=0.82), ilk 24 saat oksijen ihtiyacı (p=0.77), tam enteral beslenmeye geçiş süresi (p=0.42) ve mortalite oranı (p=0.35) arasında iki grup arasında anlamlı fark yoktu. Antenatal MgSO4 alan grupta ilk 24 saat ortalama KTA daha düşüktü (p=0.02) ancak ortalama >120/dk idi (Tablo 2).

Tablo 2. Çalışma gruplarının doğum sonrası serum elektrolitlerinin ve kardiyopulmoner fonksiyonlarının karşılaştırılması

	Antenatal magnezyum kullanımı		*p value*
	Vaka (n=78)	Kontrol (n=78)	
İlk 24 saat ;			
FiO_2 ihtiyacı (%)*	28.18±7.58	29.33±7.30	0.77
Kalp tepe atımı (/dk)*	132.9±13.85	146.1±12.85	0.02
Hipotansiyon varlığı, s (%)	10(12.8)	15 (19.2)	0.22
Mekanik ventilasyon, s (%)	31(39.7)	30(38.4)	0.82
Serum elektrolitleri			
Magnezyum (mg/dL)*	2.77±0.62	2.02±0.3	<0.01
Sodyum (mg/dL)*	135.9±3.38	136.7±3.35	0.27
Potasyum (mmol/L)*	4.62±0.56	4.37±0.82	0.65
Kalsiyum (mmol/L)*	8.43±1.9	8.3±1.1	0.53

p<0.05 anlamlı kabul edildi

*Ortalama ± Standart sapma, †Ortanca (minimum-maksimum)

TARTIŞMA

Bu retrospektif vaka-kontrol çalışmasında fetal nöroprotektif amaçla antenatal MgSO4 uygulanan preterm bebeklerle uygulanmayan grup arasında doğum sonrası 1. ve 5. dakika APGAR skorları ve doğum salonunda entübasyon ihtiyacında belirgin fark olmadığı görüldü. Ayrıca çalışmamızda iki grup arasında ilk 24 saatte ortalama oksijen ihtiyacı, hipotansiyon varlığı ve mekanik ventilatör ihtiyacı arasında belirgin fark saptanmadı. Ancak antenatal MgSO4 uygulanan grupta ilk 24 saat içinde ortalama kalp tepe atımı anlamlı olarak daha düşüktü.

Hipermagnezeminin daha büyük çocuklarda ve erişkinlerde letarji, kas güçsüzlüğü, hipotansiyon, apne, koma, kardiyak arrest ve ölüm gibi ciddi klinik sonuçları gösterildiği için antenatal MgSO4 uygulamasının çok küçük preterm bebeklerde doğum sonrası hipotoni ve solunum depresyonu riskini artırabileceğine dair endişeler vardır (15). Daha önce yapılan çalışmalar farklı gestasyon yaşı aralığında ve farklı doz antenatal MgSO4 uygulanan pretermleri dahil etmiş ve birbiri ile çelişen sonuçlar ortaya çıkmıştır (16-19). Yapılan çoğu çalışma bizim çalışmamıza benzer olarak doğum sonrası APGAR skoru, doğum salonunda entübasyon ihtiyacı, inotrop tedavisi gerektiren hipotansiyon varlığı ve doğum sonrası erken dönemde mekanik ventilasyon ihtiyacı arasında anlamlı fark saptamamıştır (17,18). Narasimhulu ve ark. çalışmasında magnezyumun doz bağımlı etki gösterdiği, serum magnezyum düzeyi 2.5 and 4.5 mg/dl olan preterm bebeklerle antenatal MgSO4 uygulanmayan pretem bebekler arasında erken dönem kardiyolpulmoner fonksiyonlar arasında fark saptanmazken serum magnezyum düzeyi >4.5 mg/dl olan preterm bebeklerde 1. dakika APGAR skorunun daha düşük olduğu ve doğum sonrası resüsitasyon ihtiyacının arttığı saptanmıştır (19). Çalışmamızda erken doğum riski olan gebelere standart düşük doz antenatal MgSO4 protokolü uygulanmış ve serum magnezyum düzeyi >4.5 mg/dl olan hasta saptanmamıştır. Erken dönem kardiyopulmoner yan etkilerinin anlamlı saptanmamasının nedeni preterm bebeklerde ortalama magnezyum düzeyinin daha düşük görülmesi olabilir.

Antenatal magnezyum sülfat uygulamasının uygulama sırasında bazal fetal kalp hızında ve varyabilite değişikliklerinde azalmaya neden olduğu gösterilmiştir (20). Paradisis ve ark. çalışmasında postnatal ilk gün içinde antenatal MgSO4 uygulanan grupta ortalama süperior vena kava akımının daha düşük olduğu, inotrop ihtiyacı arasında fark bulunmasa da bu grupta volüm genişletici ihtiyacının daha fazla olduğunu saptamıştır (21). Aynı zamanda bu çalışmada bizim çalışmamıza zıt olarak ilk 10 saat içinde kalp hızı antenatal MgSO4 maruz kalmayan pretermlere göre daha yüksek bulunmuştur. Çalışmamızda antenatal magnezyum sülfat verilen grupta ortalama kalp hızı daha düşük ancak normal aralıkta saptanmıştır. Bu çalışmada volüm genişleticilerin daha sık kullanılması ve inotrop desteğinin çalışmamıza göre daha yüksek oranda olması ortalama kalp hızının ilk saatlerde daha yüksek olmasına neden olmuş olabilir.

Neonatal non-oligurik hiperkalemi çok küçük prematüre bebeklerde, ilk 24-72 saat içinde, ekzojen potasyum alımı ve böbrek yetmezliği olmadan da potasyumunun intraselüler alandan ekstraselüler alana geçisi sonrası görülebilir (22). Bunun yanında neonatal hipermagnezeminin Na+/K+ pompasını inhibe ederek bu potasyum iyonu geçisini daha da artırdığı gösterilmiştir (23). Antenatal MgSO4 uygulamasını erken başlangıçlı neonatal hiperkalemi ile ilişkilendiren yayınlar vardır (24). Çalışmamızda antenatal MgSO4 uygulanan grupta ortalama potasyum düzeyi daha yüksek olarak bulunsa da bu istatistiksel olarak anlamlı seviyeye ulaşmamıştır. Ayrıca serum potasyum düzeyi > 6.0 mmol/L olan vaka yoktur. Serum sodyum ve kalsiyum düzeyleri de iki grup arasında benzer olarak bulunmuştur. Bunun nedeni bu çalışmada düşük doz antenatal MgSO4 protokolü uygulanmış olması olabilir. Yakın zamanda yapılan bir sistemik derleme ve meta –analiz çalışması çalışmamıza benzer şekilde antenatal MgSO4 uygulaması ile neonatal morbiditeler; PDA, NEK, İVK/PVL, ROP ve mortalite arasında bir ilişki olmadığını göstermiştir (25).

Çalışmamızın kısıtlılıkları mevcuttur. Hastaların gebelik yaşı ve doğum ağırlıkları benzer olsa da çalışma tek merkezli ve retrospektif yapılan bir çalışmadır. Erken doğum nedeni, antenatal MgSO4 başlangıç zamanı ve tam olarak kaç saat uygulandığı belirtilmemiştir. Aynı zamanda serum elektrolitleri ilk 48 içinde alınmış, doğum sonrası kord kanından düzey bakılmamıştır. Bu durum serum magnezyum değerlerinin daha düşük çıkmasına neden olmuş olabilir.

Sonuç olarak çalışmamız düşük doz nöroprotektif amaçlı antenatal MgSO4 uygulamasının, kısa dönemde neonatal morbiditeyi artırmadığını ve güvenilir olduğunu göstermiştir. Uzun dönemde amaçlanan nöroprotektif etkisini değerlendirmek için daha geniş prospektif çalışmalara ihtiyaç vardır.

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Utilization and Diagnostic Value of CA-15.3 Test in Breast Cancer: Insights from a Longitudinal Study Based on Turkish Ministry of Health Data

CA-15.3 Testinin Meme Kanserinde Kullanımı ve Tanı Değeri: Türkiye Sağlık Bakanlığı Verilerine Dayanan Bir Longitudinal Çalışmadan Elde Edilen Bilgiler

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ÖZ

Amaç: Bu çalışmanın amacı, meme kanseri izleme ve tedavisinde CA-15.3 testinin kullanımını analiz etmek ve farklı popülasyonlar arasındaki örüntülerini değerlendirmektir.

Gereç ve Yöntem: 2017-2021 yılları arasındaki beş yıllık döneme ait veriler toplandı ve bunlar arasında 2.981.142 kişiden alınan 21.579.044 CA-15.3 testi bulunmaktadır. Verilerin analizi için tanımlayıcı istatistikler kullanıldı, bunlar arasında test sayıları, nüfusa göre test oranları, referans aralığının üzerinde olan oranlar ve kanser tanısı oranları bulunmaktadır.

Bulgular: Çalışma, 2017'den 2019'a kadar CA-15.3 testinin istek sayısında artış eğilimi olduğunu ortaya koydu, bunu 2020 ve 2021 yılında önemli bir düşüş izledi. Test daha sık olarak kadınlar için istendi, özellikle 18-64 yaş grubunda. CA-15.3 testine tabi olan bireylerde kanser teşhisi oranı yıllar içinde artan bir eğilim gösterdi. İstanbul, test istek oranının en yüksek olduğu şehir olarak belirlendi, onu Ankara ve İzmir izledi. Üniversite hastaneleri en fazla test talep eden kurumlar oldu, onları devlet hastaneleri, özel hastaneler ve eğitim ve araştırma hastaneleri takip etti.

Sonuç: Bu çalışma, meme kanseri tedavisinde CA-15.3 testinin kullanım örüntülerine değerli bir bakış sunmaktadır. Test, test taleplerinde ve kanser teşhisi oranlarında artan bir eğilim gösterirken, sonuçların yorumlanmasında potansiyel kısıtlamalar nedeniyle dikkatli olunmalıdır. CA-15.3 düzeyleri ile kanser teşhisi arasındaki ilişkinin kesin bir anlayışını sağlamak için daha fazla araştırmaya ihtiyaç vardır. Bulgular, test sonuçlarının kişiselleştirilmiş yorumlanmasının önemini vurgulamakta ve bu bulguların doğrulanması için kapsamlı çalışmalara ihtiyaç olduğunu vurgulamaktadır.

Anahtar kelimeler: CA-15.3, Tümör Belirteci, Meme Kanseri, İzleme, Kullanım Modelleri, Test İstemleri, Kanser Teşhisi

ABSTRACT

Aim: The objective of this study was to analyze the utilization of the CA-15.3 test for breast cancer monitoring and treatment and evaluate its patterns across different populations.

Materials and Method: Data from a five-year period (2017-2021) were collected, including 21.578.044 CA-15.3 tests from 2.981.142 individuals. Descriptive statistics were used to analyze the data, including test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates.

Results: The study revealed an increasing trend in the number of CA-15.3 tests requested from 2017 to 2019, followed by a significant decrease in 2020 and 2021. The test was more frequently requested for women, particularly in the age group of 18-64. The rate of cancer diagnosis in individuals undergoing the CA-15.3 test also showed an upward trend over the years. Istanbul had the highest test request rate, followed by Ankara and Izmir. University hospitals requested the most tests, followed by state hospitals, private hospitals, and training and research hospitals.

Conclusion: The study provides valuable insights into the utilization patterns of the CA-15.3 test in breast cancer management. While the test showed an increasing trend in test requests and cancer diagnosis rates, caution should be exercised in interpreting the results due to potential limitations. Further research is needed to establish a definitive understanding of the relationship between CA-15.3 levels and cancer diagnosis. The findings emphasize the importance of personalized interpretation of test results and the need for comprehensive studies to validate these findings.

Keywords: CA-15.3, Tumor Marker, Breast Cancer, Monitoring, Utilization Patterns, Test Requests, Cancer Diagnosis

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INTRODUCTION

The cancer antigen CA-15.3 is a protein derived from the Mucin-1 (MUC-1) gene. Although it is primarily found in epithelial cells, it has high serum levels in 90% of patients with breast cancer (1).

CA-15.3, also known as Cancer Antigen 15.3, is a tumor marker often utilized in the monitoring and treatment of breast cancer patients. Levels in the blood typically fluctuate in conjunction with disease progression or response to treatment. Elevated CA-15.3 levels are generally observed in patients with advanced breast cancer, although certain other types of cancer or specific diseases and conditions may also elevate this level (2).

However, it is important to underscore that the CA-15.3 level does not always accurately reflect the presence or treatment response of cancer, and hence, should be used in combination with other diagnostic and monitoring tools. Nonetheless, given its widespread use and its potential to provide valuable insights into disease status, the evaluation of CA-15.3 serum levels in breast cancer patients remains a topic of ongoing research and discussion (3).

Breast cancer is the neoplasm with the highest incidence and mortality in women. As a result, several tumor markers (CA-15.3, Carcinoembryonic Antigen (CEA), serum human epidermal growth factor receptor 2 (HER2), tissue polypeptide antigen (TPA), tissue-specific antigen (TPS)) have been studied, among which CA-15.3 is the most valuable (4).

In a retrospective study involving 2.062 untreated primary breast cancer patients, the sensitivity of CEA was 12,7%, and that of cancer antigen 125 (CA-125) was 19,6%. However, when considered together, the rate increased to 28% (5).

Despite this, clinical guidelines do not recommend the use of these tumor markers for breast cancer screening due to their low sensitivity (6). When evaluated in relation to disease spread, they are mentioned as potentially useful for staging; The European Group on Tumor Markers (EGTM) supports the use of both tumor markers for detecting subclinical metastases, prognosis, and staging in patients diagnosed with local breast cancer (7).

The study of serum CA-15.3 levels is crucial as it offers a non-invasive approach to monitoring disease progression and response to treatment. Yet, its efficacy and specificity have been a subject of debate. While some studies suggest a high correlation between CA-15.3 levels and disease status, others show considerable variability. Hence, understanding the role and reliability of CA-15.3 in breast cancer management is essential, which will also be the focus of our study.

MATERIALS AND METHOD

Data from a five-year period (2017-2021) were analyzed, including a total of 21.578.044 tests from 2.981.142 individuals (Table 1). The test counts, test rates per population, and rates of exceeding the reference range were assessed based on gender, age groups, geographic regions, and healthcare institution types.

The CA-15.3 test results were obtained through the immunoassay method and extracted from the data transferred to the National Health Database System of the Turkish Ministry of Health. The healthcare database service in Türkiye is referred to as e-nabiz. The transmission of health data set packages is facilitated through Extensible Markup Language (XML) web services. This database encompasses the health records of patients who have sought medical services from all public, private, and university healthcare institutions in Türkiye, including their demographic characteristics, laboratory data, medication usage, and comorbidities.

Database and e-Pulse

e-Pulse is a platform developed by the Ministry of Health in Türkiye, allowing individuals to store and manage their health information digitally. For this study, patient information and health records were collected from the e-Pulse system. During the data collection process, personal information was protected and the principle of privacy was fully respected.

SKRS and ICD Codes

Health Coding Reference Server (SKRS) is a data recording and reporting system used by the Ministry of Health in Türkiye. This system aids in the more effective management of health services. In this study, data pulled from the SKRS and International Statistical Classification of Diseases and Related Health Problems (ICD) codes were used to analyze disease diagnoses, treatment plans, and the overall state of health services.

ICD codes are a standard disease and health problem classification system created by the World Health Organization and used worldwide. These codes are an important tool for identifying, monitoring, and treating diseases.

Data Collection:

The data were collected from medical records and laboratory databases. The information included demographics (gender, age), test requests, test results, cancer diagnoses, and healthcare institution types.

Study Population:

The study population consisted of individuals who underwent CA-15.3 testing during the study period. Both men and women were included in the analysis.

Data Analysis

Descriptive statistics were used to analyze the data. The test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates were calculated and compared across different variables, including gender, age groups, geographic regions, and healthcare institution types.

Ethical Considerations

The study adhered to ethical guidelines and protected the privacy and confidentiality of the individuals included in the data. Institutional review board approval was obtained, and all data were anonymized to ensure privacy. . Relevant approval was obtained from the Turkish Ministry of Health with the waiver of informed consent for retrospective data analysis (95741342-020/27112019).

RESULTS

Between 2017 and 2021, the CA-15.3 test was requested from 2.981.142 people, with a total of 21.579.044 tests conducted. The average number of tests per person is 7,26. while the number of tests per 100.000 population is 26.112 Among all the tumor **markers used in our CA-15.3 study, it ranks 4th in terms of the number of tests per 100.000 population (Table 1).**

Table 1. Total Consumption of Tumor Markers Between 2017-21 and Number of Tests and the Ratio of the Population by Years.

	2017		2018		2019		2020		2021	
	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
CA 15.3	4.158.853	5.146	4.726.395	5.764	5.161.865	6.208	3.646.912	4.362	3.885.019	4.646

Number of Tests	Number of Applications	Number of People	Number of Tests Per Person	Number of Tests Per 100.000 Population
21.579.044	4.077.373	2.981.142	7,24	26.112

Just like in the general population, the number and rate of tests requested for women increased as the years progressed from 2017 to 2019, but there was a significant decrease in 2020 and 2021. In all years, it ranked third among the tumor markers examined in women (Table 2).

Table 2. Number of Test Requests in Women and Men by Years.

	2017		2018		2019		2020		2021	
CA 15.3	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
Women	3.288.303	8.165	3.759.147	9.199	4.125.907	9.958	2.911.983	6.983	3.092.124	7.415
Men	870.55	2.148	967,248	2.351	1.035,951	2.483	734,929	1.753	792,895	1.892

The number of tests requested for men also increased with the progression of the year from 2017 to 2019, just like in the general population, but decreased significantly in 2020 and 2021 (Table2). When the number of tests for women/men is proportioned by year, the ratio is 3,77 in 2017, 3,88 in 2018, 3,98 in 2019, 3,96 in 2020, and 3,89 in 2021.

When the numbers of tests requested by age groups are compared by year, CA-15.3 was requested most often in the 18-64 age range, second most frequently in those over 65, and least frequently in the 0-17 age range. The ratio of the number of tests requested for the 18-64 age group to the over 65s is 3,00 in 2017, 2,97 in 2018, 2,85 in 2019, 2,92 in 2020, and 2,84 in 2021. The test consumption rate per 100.000 individuals between the 18-64 age group and those over 65 is 1/2,46 in 2017, 1/2,43 in 2018, 1/2,44 in 2019, 1/2,27 in 2020, and 1/2,45 in 2021. The number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all age groups, but showed a significant decrease in 2020-2021 (Table 3).

Table 3. Number of Test Requests by Years and Test Consumption Per 100.000 Persons by Years and Age Groups.

CA 15.3	2017			2018			2019			2020			2021		
Number of Test Requests	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	45.941	3.085.073	1.027.839	48.402	3.499.817	1.178.173	49.458	3.786.453	1.325.954	27.751	2.697.698	921.458	26.609	2.816.845	1.041.565
Test Consumption Per 100.000 Persons	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	201	6.045	14.906	211	6.744	16.395	216	7.181	17.561	122	5.099	11.585	117	5.324	13.096

When the rates of receiving a cancer diagnosis at any time in patients for whom the CA-15.3 tumor marker was requested are compared, the cancer detection rate increased as the years progressed from 2017 to 2020, with 32% of individuals diagnosed with cancer in 2017, 43% in 2020, and 38% in 2021 (Table 4).

Table 4. Percentage Distribution of Who Required Tumor Markers were Diagnosed with Cancer at Any Time.

	2017		2018		2019		2020		2021	
CA 15.3	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Dıagnosıs Of Cancer	Dıagnosıs Of Cancer
	68%	32%	66%	34%	64%	36%	57%	43%	62%	38%

Among the individuals for whom tumor markers were requested, CA-15.3 ranks third in terms of diagnosis percentage in all years.

When the times of test requests of individuals for whom tumor markers were requested are analyzed at the time of diagnosis, it was found that the tests were requested most frequently before the diagnosis in all years, second most frequently at the same time as the diagnosis, and least frequently after the diagnosis. The rate of test requests before the diagnosis increased as the years progressed until 2020, with a rate of 13,88% in 2017, 33,98% in 2020, and 31,41% in 2021. When the test request rates according to diagnosis times are compared with each other (before diagnosis/at the same time as diagnosis/after diagnosis), it was found that there was no significant difference between the years 2017-2021.

When the utilization rates of CA-15.3 by provinces are compared, it was found that it was requested the most in Istanbul in all years, followed by Ankara, and then Izmir. The number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all provinces, but showed a significant decrease in 2020-2021. When the numbers of tests requested by years are compared by provinces, the rate of tests requested in 2017 was 2,47%, while the rate in 2021 was 1,87%. The percentage of the total number of tests requested from 2017 to 2021 was found to be 9,13% in Istanbul, 4,53% in Ankara, and 2,76% in Izmir. These three cities constitute 16,42% of the total requests.

The CA-15.3 test was most frequently requested from university hospitals, followed by state hospitals, private hospitals, and finally training and research hospitals. In all years, the number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all hospitals, but showed a significant decrease in 2020-2021.

When the regions were analyzed based on the number of tests per 100.000 population, the highest demand was in the Eastern Anatolia region in 2017, in the Marmara region in 2018, and in the Central Anatolia region between 2019-2021. The lowest region is the Southeast Anatolia region. In 2021, when the Central Anatolia region, which has the highest test ratio, was compared with the Marmara region in the second rank, the ratio was 1,10, and when compared with the Southeast Anatolia region, which is the lowest, the ratio was 4,31.

When compared based on the number of tests per person, the highest distribution belongs to the Eastern Anatolia region in all years. The second rank belongs to the Central Anatolia region in 2019, and the Aegean region in other years. The region with the lowest distribution is the Southeast Anatolia region. In 2021, when the Eastern Anatolia region, which has the highest distribution, is compared with the Southeast Anatolia region, which has the lowest distribution, the result is 1,16 (Table 6).

Year	Related Cancer Diagnosis		Non-related Cancer Diagnosis		Total Number of People Tested
2017	154.290	19,36%	203.602	25,54%	797.085
2018	175.084	19,49%	246.877	27,49%	898.101
2019	192.828	20,14%	273.485	28,56%	957.420
2020	184.974	27,13%	251.682	36,91%	681.849
2021	190.387	25,63%	252.089	33,93%	742.918

2017		2018		2019		2020		2021	
EASTERN ANATOLIA REGION	6.588	MARMARA REGION	6.927	CENTRAL ANATOLIA REGION	7.550	CENTRAL ANATOLIA REGION	5.467	CENTRAL ANATOLIA REGION	6.089
MARMARA REGION	6.315	CENTRAL ANATOLIA REGION	6.509	MARMARA REGION	7.423	MARMARA REGION	5.230	MARMARA REGION	5.517
AEGEAN REGION	5.746	EASTERN ANATOLIA REGION	6.439	AEGEAN REGION	6.661	AEGEAN REGION	5.016	AEGEAN REGION	5.295
CENTRAL ANATOLIA REGION	5.390	AEGEAN REGION	6.126	EASTERN ANATOLIA REGION	6.381	EASTERN ANATOLIA REGION	3.999	EASTERN ANATOLIA REGION	4.326
BLACK SEA REGION	4.746	BLACK SEA REGION	5.386	BLACK SEA REGION	5.454	BLACK SEA REGION	3.716	BLACK SEA REGION	4.068
MEDITERRANEAN REGION	3.493	MEDITERRANEAN REGION	4.464	MEDITERRANEAN REGION	4.957	MEDITERRANEAN REGION	3.430	MEDITERRANEAN REGION	3.478
SOUTHEAST ANATOLIA REGION	2.053	SOUTHEAST ANATOLIA REGION	2.350	SOUTHEAST ANATOLIA REGION	2.243	SOUTHEAST ANATOLIA REGION	1.426	SOUTHEAST ANATOLIA REGION	1.412

When cities are analyzed based on the number of test requests, Istanbul is the city where the most tests are requested in all years, and the second city is Ankara. Izmir and Bursa are in the third and fourth places. When the number of tests per 100.000 population is examined, Sinop is in 2017, Erzurum in 2018 and 2020, Kırşehir in 2019, and Isparta in 2021. The top 3 cities with the highest test request rate, Istanbul, Ankara, and Izmir, are not among the top 7 cities with the number of tests per 100.000 population.

When clinics are compared based on the number of test requests, the clinic that requests the most tests is the Obstetrics and Gynecology clinic between 2017-2019, and the Medical Oncology clinic in 2020-2021. The second place belongs to the Internal Diseases clinic between 2017-2019, and the Obstetrics and Gynecology clinic in 2020 and 2021. Medical oncology is in the 3rd place between 2017-2019, and it is in the first ranks in 2020-2021. Family medicine is in the 7th place in 2017 and 2018, 6th place in 2019, and 7th place in 2020 and 2021; The Emergency Medicine clinic is in the 8th place between 2017-2020, and it is in the 9th place in 2021 (Table 7).

2017		2018		2019		2020		2021	
GYNECOLOGY AND OBSTETRICS	916.840	GYNECOLOGY AND OBSTETRICS	1.036.325	GYNECOLOGY AND OBSTETRICS	1.093.072	MEDICAL ONCOLOGY	924.438	MEDICAL ONCOLOGY	873.601
INTERNAL MEDICINE	876.543	INTERNAL MEDICINE	946.663	INTERNAL MEDICINE	993.719	GYNECOLOGY AND OBSTETRICS	715.967	GYNECOLOGY AND OBSTETRICS	750.126
MEDICAL ONCOLOGY	633.224	MEDICAL ONCOLOGY	799.195	MEDICAL ONCOLOGY	946.918	INTERNAL MEDICINE	593.676	INTERNAL MEDICINE	721.656
GENERAL SURGERY	543.217	GENERAL SURGERY	585.203	GENERAL SURGERY	576.742	GENERAL SURGERY	375.894	GENERAL SURGERY	394.454
RADIATION ONCOLOGY	169.682	RADIATION ONCOLOGY	196.353	RADIATION ONCOLOGY	200.664	GASTROENTEROLOGY	128.543	GASTROENTEROLOGY	145.908
GASTROENTEROLOGY	144.894	GASTROENTEROLOGY	172.382	FAMILY MEDICINE	187.641	RADIATION ONCOLOGY	120.578	RADIATION ONCOLOGY	116.435
FAMILY MEDICINE	122.378	FAMILY MEDICINE	162.032	GASTROENTEROLOGY	167.706	FAMILY MEDICINE	100.988	FAMILY MEDICINE	111.427
EMERGENCY MEDICINE	76.121	EMERGENCY MEDICINE	83.753	EMERGENCY MEDICINE	113.161	EMERGENCY MEDICINE	82.965	GYNECOLOGICAL ONCOLOGY SURGERY	84.514
NEUROLOGY	57.089	NEUROLOGY	65.882	GYNECOLOGICAL ONCOLOGY SURGERY	86.165	GYNECOLOGICAL ONCOLOGY SURGERY	67.442	EMERGENCY MEDICINE	84.334
CHEST DISEASES	55.133	UROLOGY	58.391	NEUROLOGY	76.157	NEUROLOGY	53.807	NEUROLOGY	64.785

When the diagnoses entered in the application where the CA-15.3 test request was made were examined, the breast malignant neoplasm diagnosis was the most frequently entered diagnosis in 2017-2018 and the second most frequently entered diagnosis in 2019 and 2021. The breast malignant neoplasm, undefined diagnosis is the most entered diagnosis in 2020, the 3rd place in 2017, and the 2nd place in 2018-2021. In 2019 and 2021, the most common diagnosis of vitamin D deficiency, undefined, was entered. In total for five years, the most common diagnosis is vitamin D deficiency, undefined; second frequently is breast malignant neoplasm, undefined; and the third place is breast malignant neoplasm. When the rates of exceeding the reference range of the test are compared by years, the highest rate is in 2021 with a rate of 9,74%, the lowest rate is in 2019 with 7,62%. When the rates of exceeding the reference range of the test are compared by institution levels, the highest rate is 9,92% in third-level institutions, followed by 7,32% in second-level institutions, and 3,73% in first-level institutions.

When the rates of exceeding the reference range by institution types are examined, the total rate is 8,76%, with the highest rate of 11,78% in university hospitals, followed by 10,00% in

private health institutions, and 8,11% in public hospitals.

When the rates of exceeding the reference range by geographical regions are examined, the highest rate is 10,9% in the Aegean region, which has the most frequent test requests in the 3rd region and has the highest number of test requests per 100.000 people in all years except 2018 (it is the Eastern Anatolia region in 2018). The Black Sea region is in the second place with a rate of 9,8%, followed by the Mediterranean region with a rate of 9,5%. The lowest rate belongs to the Southeastern Anatolia region, which has the lowest number of test requests and the lowest number of test requests per 100.000 people, with a rate of 5,0%.

When the rates of exceeding the reference range by gender are examined, the overall positive rate is 8,73%, with 9,67% in men and 8,55% in women.

When the rates of exceeding the reference range by age groups are examined, the highest rate is in those over 65 with 12,95%, followed by the 18-64 age group with a rate of 7,40%, and the 0-17 age group with a rate of 1,22%. When the age groups are ratioed, the positivity rates are 10,6/6,06/1.

When the rates of exceeding the reference range by admission status are examined, it is most frequently requested from outpatient patients with a rate of 12,10%, followed by inpatients with a rate of 11,35%, and outpatients with a rate of 8,22%. When ratioed in order, the ratio is calculated as 1,47/1,38/1. Among the tumor markers examined in the study, all markers exceeded the reference range at a higher rate in inpatients, while CA-15.3 is higher in outpatient patients.

When the rates of exceeding the reference range by cancer diagnosis status are examined, a total of 8,77% of people tested positive, and of those who tested positive, 15,98% have a cancer diagnosis, while 4,17% do not have a cancer diagnosis.

When the rates of tests that exceed the reference range from the clinics requesting the CA-15.3 test are examined; the highest rate is in the Medical Oncology clinic with 19,59%, followed by the Gastroenterology clinic with 9,21%, and the Gynecological Oncology Surgery with 9,20%. In the Obstetrics and Gynecology clinic, which had the highest number of test requests between 2017-2019, the rate is 3,47%, in the Medical Oncology clinic, which had the highest number between 2020-2021, the rate is 19,59 (first place), and in Internal Diseases, which was in the second place between 2017-2019, the rate is 7,14%. The rate in Family Medicine is 4,70%.

When the distribution of test costs by years is examined, the sut cost in 2017 is 33.270.824 TL, the unit cost is 16.392.207 TL, and in 2021 the sut cost is 31.080.152 TL, the unit cost is 15.312.884 TL.

DISCUSSION

This study presents a detailed analysis of the use of the CA-15.3 test between 2017 and 2021. A total of 21.579.044 tests were applied to 2.981.142 individuals, which translates to 26.112 tests per 100.000 individuals. Increasing numbers and rates of tests over the years have shown that this test has risen to 4th place among tumor markers. When viewed by gender, a similar trend has been observed in both women and men: the numbers and rates of tests increased from 2017 to 2019, but a significant decline was seen in 2020 and 2021. In women, the CA-15.3 test has ranked third among all tumor markers examined each year.

When examining the use of the test by age groups, it is found that the CA-15.3 test was most frequently requested from individuals aged 18-64. This age group is followed by individuals over 65 years and leastly by the 0-17 age range. These findings demonstrate the impact of the test on the general population, as well as individuals with specific demographic characteristics.

Breast cancer is the most common and deadly type of cancer among women worldwide and in Türkiye. According to World Health Organization data from 2018, the incidence of breast cancer worldwide in 2018 was 2.000.088. In Türkiye, the incidence is 50/100.000 and the 2018 incidence was 22.500 (8).

In our study, when the rate of receiving a cancer diagnosis at any time was compared in patients for whom the CA-15.3 tumor marker was requested, the cancer detection rate increased as the years progressed from 2017 to 2020. In 2017, 32% of individuals received a cancer diagnosis, 43% in 2020, and 38% in 2021. When the rates of cancer detection were compared in individuals for whom tumor markers were requested, CA-15.3 ranked third in diagnosis percentage every year.

Approximately 1% of breast cancer occurs in men (9). In our study, when the female/male test number ratio was compared over the years, the ratio was 3,77 in 2017, 3,88 in 2018, 3,98 in 2019, 3,96 in 2020, and 3,89 in 2021. In all years, it ranks third among tumor markers tested in women. Additionally, when rates of exceeding the reference range were examined by gender, overall 8,73% were positive, with 9,67% in men and 8,55% in women being positive.

Several studies have shown that high levels of CEA in primary breast cancer lead to a poor prognosis, and similarly, the presence of high CA 15.3 levels at the time of diagnosis is associated with a higher stage of breast cancer, tumor size, lymph node involvement, and lower survival (10,11).

In our study, when the timing of test requests for individuals who had tumor markers requested was analyzed at the time of diagnosis, requests were most frequent prior to diagnosis in all years, second most frequent at the same time as diagnosis, and least frequent after diagnosis. A study conducted by Hou and colleagues showed that it had a sensitivity of 7% in early disease. The same study also evaluated the sensitivity of CA 15.3 in metastatic breast cancer as 82,8% (12).

In our study, in 2017, 19,36% of individuals who had the CA-15.3 test received a diagnosis of a cancer associated with CA-15.3, while 25,54% received a diagnosis of a cancer not associated with CA-15.3. This rate increased until 2020, when 27,13% of patients were diagnosed with a cancer associated with CA-15.3 and 36,91% were diagnosed with a cancer not associated with CA-15.3. In 2021, these rates were 25,63% and 33,93%, respectively.

When the rates of tests exceeding the reference range were examined by the status of receiving a cancer diagnosis, in total 8,77% of tests were positive, with 15,98% of positive tests belonging to individuals with a cancer diagnosis and 4,17% to individuals without a cancer diagnosis.

In a study conducted by Tampellini and colleagues on 526 patients diagnosed with metastatic breast cancer, the time until progression was evaluated in relation to CA-15.3 levels. The time was 15,3 months in patients with normal CA-15.3 levels, 11,7 months in patients whose levels initially rose then fell by 25%, 9,6 months in patients with high levels, and 8,6 months in patients whose levels increased (13).

Breast cancer is more common in the western regions of Türkiye (40-50/100.000) compared to the eastern regions (20/100.000). It is thought that the reasons for this are a higher rate of hormone therapy use, shorter lactation period, dietary habits, and the adoption of a western lifestyle in our western regions (14).

In our study, when regions were analyzed based on the number of tests per 100.000 people, the highest number of requests was in the Eastern Anatolia region in 2017, in the Marmara region in 2018, and in the Central Anatolia region between 2019-2021. The region with the lowest number is Southeastern Anatolia. When compared based on the number of tests per person, the highest distribution in all years belongs to the Eastern Anatolia region.

In the USA, 5,6% of patients diagnosed with invasive breast cancer between 2000-2014 were under the age of 40 (15).

When comparing the rates of cancer diagnosis in patients who had the CA-15.3 tumor marker requested, the cancer detection rate increased from 2017 to 2020. Among individuals who had tumor markers requested, the CA-15.3 ranked third each year in terms of diagnosis percentage.

Considering the CA-15.3 test requests and rates of exceeding the reference range according to years, geography, type of institution, clinic, and patient condition, it is clear that further analysis is required to understand how these factors affect the use and results of the test. In particular, the rates of test results exceeding the reference range have varied significantly. These findings contribute to a broader understanding of how an individual's demographic characteristics and health status can affect test results. In light of these results, it underscores the importance of an individualized approach in interpreting test results.

In our study, when test request numbers were compared by age groups over the years, CA-15.3 was most frequently requested in the 18-64 age range, second most in individuals over 65 years, and least frequently in the 0-17 age range.

When rates of exceeding the reference range were examined based on the admission status, the rates were highest in outpatients, second highest in inpatients, and lowest in walk-in patients.

This study may have several potential limitations. First, the accuracy and consistency in collecting and recording data of patients undergoing CA-15.3 tumor marker tests could directly influence the outcomes, with any errors in data collection and analysis possibly skewing results. Second, the study's retrospective design, which uses existing data, is prone to biases and various errors, which could lead to misrepresented findings. Third, the lack of a control group can make interpreting the results difficult, as control groups provide an objective benchmark for comparison in studies and experiments. Fourth, the study design might overlook the influence of certain confounding factors, such as the patients' genetic history, lifestyle factors, or the presence of other diseases, which could affect the outcomes. Lastly, the study's statistical power, which determines whether the results are statistically significant, can be misleading if it's low. In summary, all these potential limitations need to be carefully considered when interpreting the study's findings.This study may have several potential limitations. First, the accuracy and consistency in collecting and recording data of patients undergoing CA-15.3 tumor marker tests could directly influence the outcomes, with any errors in data collection and analysis possibly skewing results. Second, the study's retrospective design, which uses existing data, is prone to biases and various errors, which could lead to misrepresented findings. Third, the lack of a control group can make interpreting the results difficult, as control groups provide an objective benchmark for comparison in studies and experiments. Fourth, the study design might overlook the influence of certain confounding factors, such as the patients' genetic history, lifestyle factors, or the presence of other diseases, which could affect the outcomes. Lastly, the study's statistical power, which determines whether the results are statistically significant, can be misleading if it's low. In summary, all these potential limitations need to be carefully considered when interpreting the study's findings.

This study may have several potential limitations. First, the accuracy and consistency in collecting and recording data of patients undergoing CA-15.3 tumor marker tests could directly influence the outcomes, with any errors in data collection and analysis possibly skewing results. Second, the study's retrospective design, which uses existing data, is prone to biases and various errors, which could lead to misrepresented findings. Third, the lack of a control group can make interpreting the results difficult, as control groups provide an objective benchmark for comparison in studies and experiments. Fourth, the study design might overlook the influence of certain confounding factors, such as the patients' genetic history, lifestyle factors, or the presence of other diseases, which could affect the outcomes. Lastly, the study's statistical power, which determines whether the results are statistically significant, can be misleading if it's low. In summary, all these potential limitations need to be carefully considered when interpreting the study's findings.

CONCLUSION

In conclusion, our study suggests that the incidence of cancer diagnosis and the levels of CA-15.3 tumor marker are closely related and have shown a general increase over the years. However, these results should be interpreted with caution due to potential limitations in the study design. More comprehensive and robust studies are necessary to establish a definitive understanding of the relationship between CA-15.3 levels and cancer diagnosis and to further validate these findings.

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Özgün Araştırma / Original Article

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Jinekolojik Kanserler Nedeniyle Opere Edilen ve Yoğun Bakımda Takip Edilen Hastalarda Polifarmasi Yatış Süresiyle İlişkili Midir?

Is Polypharmacy Related to the Intensive Care Unit Length of Stay in Patients Who Have Been Operated on Due to Gynecological Cancers?

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ÖZ

Amaç: Jinekolojik kanserler nedeniyle opere edilen hastalarda, hastaların operasyon öncesinde kullandığı ilaç sayısı ve potansiyel uygunsuz ilaç kullanımının yoğun bakım yatış süresiyle ilişkili olup olmadığını değerlendirmektir.

Gereçler ve Yöntem: Çalışmaya 2020 Haziran ve 2022 Aralık tarihleri arasında Ankara Bilkent Şehir Hastanesi Jinekolojik Onkoloji Cerrahisi Kliniği'nde endometrium, over, serviks ve diğer jinekolojik kanserler nedeniyle opere edilen ve operasyon sonrasında en az 24 saat yoğun bakımda takip edilen hastalar, retrospektif olarak dahil edilmiştir. Polifarmasi, 5 ve üzerinde ilaç kullanımı olarak tanımlanmıştır. Uygunsuz ilaç kullanımı için Türkiye Yaşlıda Uygunsuz İlaç Kullanım Kriterleri (TIME-to-STOP, TIME-to-START) kullanılmıştır.

Bulgular: Çalışmaya toplam 253 hasta dahil edilmiştir. 220 (%87) hasta endometrium kanseri, 25 (%9.9) hasta over kanseri, 2 (%0.8) hasta serviks kanseri, 6 (%2.4) hastada diğer jinekolojik kanserler nedeniyle opere edilip yoğun bakımda postoperatif takip edilmiştir. Hastalar postoperatif dönemde yoğun bakımda 2 gün (aralık; 1-21 gün) takip edilmiştir. Polifarmasi 34 (%13.4) hastada, potansiyel uygunsuz ilaç kullanımı ise 83 (%32.8) hastada bulunmuştur. Yoğun bakım yatış süresi ve ilaç sayısı arasında pozitif bir korelasyon izlenmiştir (r=0.142; p=0.024). Çok değişkenli regresyon analizinde, ilaç sayısı (OR:1.228 %95 CI:1.034-1.460, p=0.020) diğer tüm nedenlerden bağımsız olarak yoğun bakımda yatış süresiyle ilişkili bulunmuştur.

Sonuç: Jinekolojik kanserler nedeniyle opere edilen ve post operatif dönemde yoğun bakımda takip edilen hastalarda, polifarmasi yatış süresiyle ilişkilidir. Hastaların yoğun bakım kalış sürelerini ön görmek için her hastada, hastaların yatış öncesi ko-morbiditeleri ve ilaç kullanımlarını değerlendirmek anahtar noktalardan biridir.

Anahtar Kelimeler: Jinekolojik Malignite, Yoğun Bakım Ünitesi, Polifarmasi, Potansiyel Uygunsuz İlaç Kullanımı

ABSTRACT

Aim: To evaluate whether the number of drugs taken by the patients before the operation or the use of potentially inappropriate medications (PIM) are associated with the length of stay in the intensive care unit (ICU) in patients with gynecological cancers.

Materials and Methods: This study included retrospectively all patients who underwent gynecological cancer surgery at the Ankara Bilkent City Hospital Gynecological Oncology Surgery Clinic between June 2020 and December 2022 and were monitored for at least 24 hours in the ICU. The use of five or more medications was defined as polypharmacy. PIM are assessed according to the Turkish inappropriate medication use in the elderly (TIME-to-STOP, TIME-to-START) criteria.

Results: A total of 253 patients were included in the study. Two hundred twenty (87%) patients underwent surgery for endometrial cancer, 25 (9.9%) for ovarian cancer, 2 (0.8%) for cervical cancer, and 6 (2.4%) for other gynecological cancers. The patients were followed up in the ICU for 2 days (range, 1-21 days). Polypharmacy and PIM were found in 34 (13.4%) and 83 (32.8%) patients, retrospectively. A positive correlation was observed between the length of stay and the number of drugs (r=0.142; p=0.024). The number of drugs (OR:1.228, 95% CI: 1.034-1.460, p=0.020) was found to be associated with the length of stay in the ICU, independent of all other causes.

Conclusion: One of the most important factors to consider when deciding how long a patient will stay in the ICU is to assess the co-morbidities and drug use of the patient.

Keywords: Gynecological Malignancy, Intensive Care Unit, Polypharmacy, Potentially inappropriate medications

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GİRİŞ

Jinekolojik kanserler nedeniyle cerrahi yapılanlarda postoperatif komplikasyonları önlemede yoğun bakım takibi anahtar rol oynamaktadır. 2023 yılı kanser istatistiklerine göre tahmini yıllık jinekolojik yeni vaka sayısı over kanseri için 19.710, endometrium kanseri için 66.200, serviks kanseri için 13.960 ve diğer jinekolojik kanserler için 14.940 olarak belirlenmiştir (1). Cerrahi ve anestezi işlemleri ve postoperatif yoğun bakım takiplerindeki gelişmeler sonrasında; jinekolojik kanser nedenli operasyonlara bağlı mortalite ve komplikasyonların sıklığında azalma görülmüştür. Postoperatif dönemde rutin yoğun bakım takibi, özellikle evreleme cerrahisi yapılan ve operasyon süresi uzun olan ileri evre over ve endometrium kanserinde gerekli görülmektedir (2).

Yaşlanmayla birlikte kronik hastalıkların sayısının artmasıyla ilaç kullanımı artmaktadır. Polifarmasi için literatürde birden çok tanım olmakla birlikte, ilaç sayısına göre bakıldığında genellikle aynı anda 5'ten fazla ilaç kullanımı olarak tanımlanmıştır (3). Polifarmasi mortalite, düşme, adverse ilaç reaksiyonları, yatış süresinde uzama ve taburculuk sonrasında tekrar yatış ve maliyet artışı ile ilişkilidir (3,4).

Postoperatif sonuçların ve yatış süresinin; hastanın yaşına, ko-morbid hastalıklarına, uygulanan cerrahi prosedüre, hastanın kan kaybı miktarına, sıvı resusitasyonu miktarına, ventilatör ihtiyacı olup olmamasına bağlı olduğu bilinmektedir (5). Polifarmasi ve uygunsuz ilaç kullanımı da yatış süresi için önemli bir faktördür (6). Özelikle kanser hastalarında ilaç sayısının yanında potansiyel uygunsuz ilaç kullanımı önemli bir sorun olmaya başlamıştır. Uygunsuz ilaç kullanımıysa hastaneye tekrar yatış, mortalite ve postoperatif morbidite ile ilişkilidir (7). Uygunsuz ilaç kullanımını belirlemek için BEERS kriterleri (8), STOPP/START kriterleri (Screening Tool of Older Person's Prescriptions) (9) ve ülkemizde oluşturulan TIME (Turkish Inappropriate Medication use in the Elderly [Türkiye Yaşlıda Uygunsuz İlaç Kullanım Kriterleri]) kriterleri kullanılabilir (10).

Bu çalışmadaki amacımız, jinekolojik kanserler nedeniyle opere edilen hastalarda, hastaların operasyon öncesinde kullandığı ilaç sayısı ve potansiyel uygunsuz ilaç kullanımının yoğun bakım yatış süresiyle ilişkili olup olmadığını değerlendirmektir.

GEREÇLER VE YÖNTEM

Çalışma Popülasyonu

Çalışmaya 2020 Haziran ve 2022 Aralık tarihleri arasında Ankara Bilkent Şehir Hastanesi Jinekolojik Onkoloji Cerrahisi Kliniği'nde endometrium, over, serviks ve diğer jinekolojik kanserler nedeniyle opere edilen ve operasyon sonrasında en az 24 saat yoğun bakımda takip edilen hastalar, retrospektif olarak dahil edilmiştir. 60 yaş altındaki hastalar, operasyon sonrası yoğun bakımda takip edilmemiş hastalar ve demografik ve klinik bilgilerine ulaşılamayan, ilaç kullanımlarıyla ilgili eksik bilgi olan hastalar çalışmadan dışlanmıştır. Çalışmanın etik kurul onayı, lokal etik kurul tarafından alınmıştır (E2-22-2760, 09.11.2022).

Verilerin Toplanması

Hastaların hastane klinik notlarından ve ulusal sağlık sistemi veri tabanından yaş, primer jinekolojik kanseri, ek hastalıkları ve kullandıkları ilaçlarla ilgili bilgiler elde edilmiştir.

Polifarmasi, 5 ve üzerinde ilaç kullanımı olarak tanımlanmıştır (3). Uygunsuz ilaç kullanımı için TIME kriterleri kullanılmıştır. TIME kriterleri ilaçların etkili olduğu sistemlere göre sınıflandırılmıştır. Genelde yaşlıda kullanılması uygun olmayan ancak klinik pratikte sıklıkla yanlışlıkla kullanılan ilaçlar TIME-to-STOP, yaşlıda sıklıkla kullanılması yararlı olan ancak klinik pratikte genellikle kullanılmayan ilaçlar da TIME-to-START kriterleri olarak belirlenmiştir (10).

İstatistiksel Analiz

Çalışmanın istatistikleri IBM SPSS Statistics 23.0 (Armonk, NY, USA) programı kullanılarak yapıldı. Tanımlayıcı istatistikler; sayısal değişkenler için ortalama±standart sapma veya ortanca (25.–75. yüzdelik dilim), kategorik değişkenler için ise sayı ve yüzde olarak ifade edildi. Gruplar arasındaki karşılaştırmalar sayısal değişkenler için normal dağılım durumuna göre t-testi veya Mann Whitney U testi ile kategorik değişkenler için ki-kare testi ile yapıldı. İlaç sayısı ve yatış süresi arasındaki korelasyonu değerlendirmek için Spearman Korelasyon Analizi kullanıldı. Çok değişkenli analizde, hipertansiyon, diabetes mellitus, depresyon, gastrit, peptik ülser ve diğer solid kanserlerin varlığı, yaş ve ilaç sayısı modele konulduktan sonra, 24 saatten daha uzun süre yoğun bakım yatışını predikte eden nedenler belirlendi. Model uyumu Hosmer-Lemeshow testi kullanılarak değerlendirildi ve birbiri arasında yüksek kolinerite olan faktörler modele dahil edilmedi. $p<0.05$ için sonuçlar istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya toplam 253 hasta dahil edilmiştir. Hastaların yaş ortalaması 67.4±6.1 yıldır. 220 (%87) hasta endometrium kanseri, 25 (%9.9) hasta over kanseri, 2 (%0.8) hasta serviks kanseri, 6 (%2.4) hastada diğer jinekolojik kanserler nedeniyle opere edilip yoğun bakımda postoperatif takip edilmiştir. Hastaların ek hastalıkları değerlendirildiğinde; 144 (%56.9) hasta hipertansiyon, 54 (%21.3) hasta diabetes mellitus, 38 (%15) hasta hipotiroidi, 31 (%12.3) hasta koroner arter hastalığı, 20 (%7.9) hasta astım ya da kronik obstruktif akciğer hastalığı, 11 (%4.3) hasta kronik böbrek hastalığı, 10 hasta (%4) nörolojik hastalık, 30 (%11.9) hasta depresyon, 32 (%12.6) hasta gastrit, peptik ülser tanılarıyla takip edilmekteydi. Çalışmaya dahil edilen 11 (%4.3) hastada ek başka bir solid kanser öyküsü vardı.

Hastalar postoperatif dönemde yoğun bakımda 2 gün (aralık; 1-21 gün) takip edilmiştir. Hastalar operasyon ve yoğun bakım öncesinde 2 adet (aralık; 0-9 adet) ilaç kullanmıştır. Polifarmasi 34 (%13.4) hastada vardır. Potansiyel uygunsuz ilaç kullanımı ise 83 (%32.8) hastada bulunmuştur.

Yatış süresi polifarmasi olan grupta 2.8 gün (aralık; 1-3 gün), olmayan grupta ise 1.9 gündür (aralık; 1-2.5 gün) ($p=0.037$) (Figür 1). Polifarmasi olan ve olmayan hasta gruplarının demografik özellikleri Tablo 1'de özetlenmiştir.

Tablo 1. Polifarmasi olan ve olmayan hasta gruplarının klinik ve demografik özellikleri

Faktörler Ortalama±SD		**Polifarmasi** Var (n=34)	**Polifarmasi** Yok (n=219)	***p***
		Ortalama±SD		
Yaş (yıl)		68.2 ± 8.8	67.2 ± 5.9	*0.404*
		Ortalama (aralık)	**Ortalama (aralık)**	
Yoğun bakım yatış günü		2.8 (1-3)	1.9 (1-2.5)	***0.037***
		n (%)	**n (%)**	
Tanı	Endometrium kanseri	31 (%91.2	189 (%86.3)	*0.716*
	Over kanseri	2 (%5.9)	23 (%10.5)	
	Serviks kanseri	0	2 (%0.9)	
	Diğer jinekolojik maligniteler	1(%2.9)	5 (%2.3)	
Hipertansiyon		33 (%97.1)	111 (%50.7)	***<0.001***
Diabetes mellitus		13 (%38.2)	41 (%18.7)	***0.010***
Koroner arter hastalığı		5 (%14.7)	26 (%11.9)	*0.582*
Kronik böbrek hastalığı		8 (%17.8)	3 (%0.8)	***<0.001***
Hipotiroidi		10 (%29.4)	28 (%12.8)	***0.012***
Astım / Kronik obstruktif akciğer hastalığı		7 (%20.6)	13 (%5.9)	***0.009***
Gastrit / Peptik ülser		4 (%11.8)	28 (%12.8)	*0.868*
Nörolojik Hastalık		5 (%14.7)	5 (%2.3)	***0.005***
Depresyon		6 (%17.6)	24 (%11)	*0.259*
Diğer solid malignite		1 (%2.9)	10 (%4.6)	*0.666*

Potansiyel uygunsuz ilaç kullanımı olan ve olmayan grupta yatış süresi benzer bulunmuştur (p=0.261). Potansiyel uygunsuz ilaç kullanımı olanlarda hipertansiyon, diabetes mellitus, kronik böbrek hastalığı ve depresyon tanıları daha sık görülmüştür. Potansiyel uygunsuz ilaç kullanımı olan ve olmayan grupların demografik özellikler Tablo 2'de özetlenmiştir.

Tablo 2. Potansiyel uygunsuz ilaç kullanımı olan ve olmayan hasta gruplarının klinik ve demografik özellikleri

Faktörler Ortalama±SD		**Potansiyel** Uygunsuz ilaç Kullanımı Var (n=83)	**Potansiyel Uygunsuz İlaç Kullanımı Yok (n=170)**	***p***
		Ortalama±SD		
Yaş (yıl)		63.9 ± 10.2	59.4 ± 9.8	***<0.001***
		Ortalama (aralık)	**Ortalama (aralık)**	
Yoğun bakım yatış günü		2.14 (1-3)	1.78 (1-2)	***0.030***
		n (%)	**n (%)**	
Tanı	Endometrium kanseri	73 (%88)	14 (%86.5)	*0.851*
	Over kanseri	8 (%9.6)	17 (%10)	
	Serviks kanseri	1 (%1.2)	1 (%0.6)	
	Diğer jinekolojik maligniteler	1 (%1.2)	5 (%2.9)	
Hipertansiyon		70 (%84.3)	74 (%43.5)	***<0.001***
Diabetes mellitus		25 (%30.1)	29 (%17.1)	***0.017***
Koroner arter hastalığı		4 (%4.8)	27 (%15.9)	***0.012***
Kronik böbrek hastalığı		7 (%8.4)	4 (%2.4)	***0.044***
Hipotiroidi		16 (%19.3)	22 (%12.9)	*0.185*
Astım / Kronik obstruktif akciğer hastalığı		6 (%7.2)	14 (%8.2)	*0.781*
Gastrit / Peptik ülser		3 (%3.6)	29 (%17.1)	***0.003***
Nörolojik hastalık		5 (%6)	5 (%2.9)	*0.304*
Depresyon		19 (%22.9)	11 (%6.5)	***<0.001***
Diğer solid malignite		2 (%2.4)	9 (%5.3)	*0.512*

Yapılan korelasyon analizinde yoğun bakım yatış süresi ve ilaç sayısı arasında pozitif bir korelasyon izlenmiştir (r=0.142; p=0.024).

Bir günden daha uzun süre yoğun bakımda yatışı etkileyen faktörlere bakıldığında, hastaların ko-morbiditelerinden ve yaştan bağımsız olarak ilaç sayısı (OR:1.228 %95 CI:1.034-1.460, p=0.020) yoğun bakımda yatış süresiyle ilişkili bulunmuştur.

TARTIŞMA

Tek merkezli, retrospektif çalışmamızda jinekolojik kanserler nedeniyle opere edilip postoperatif yoğun bakımda takip edilenlerde polifarmasi oranı %13.4, potansiyel uygunsuz ilaç kullanımı ise %32.8 oranında izlenmiştir. İlaç sayısı diğer tüm ek hastalıklardan bağımsız olarak yoğun bakım kalış süreleriyle ilişkili bulunmuştur.

Polifarmasi yoğun bakım ve geriatri servislerinde takip edilenlerde sık görülmektedir. 1200 hastanın dahil edildiği bir çalışmada potansiyel uygunsuz ilaç kullanım oranı çalışmamıza benzer şekilde %30 oranında bulunmuş ve uygunsuz ilaç kullanımı ile hastane yatış süresi arasında diğer nedenlerden bağımsız bir ilişki görülmüştür (11). Yoğun bakımda takip edilen 23.844 hastanın değerlendirildiği bir çalışmada polifarmasi %30 oranında görülmüş ve taburculuk sonrasında polifarmasi olanlarda olmayan gruba göre 1 yıl içindeki acil tekrar yatış %22 daha fazla bulunmuştur (12). Bizim çalışmamızda da ilaç sayısı yatış süresiyle ilişkili bulunmuştur.

Akciğer, gastrointestinal sistem, meme ve jinekolojik kanserler nedeniyle primer veya adjuvan tedavi alanlarda planlanmamış hastane yatışını değerlendiren ve %14'ünü jinekolojik kanserlerin oluşturduğu bir çalışmada, polifarmasi hastaneye beklenmeyen yatışlarıyla ilişkili bulunmuştur (13). 236 over kanserinin dahil edildiği bir çalışmada, hastaneye yatan hastalarda potansiyel ilaç etkileşimleri ve polifarmasi arasında bir ilişki görülmüştür. Ancak bizim çalışmamızdan farklı olarak; ilaç etkileşimleri ve yatış süresi arasında anlamlı bir ilişki gözlenmemiştir (14). Oldak S ve arkadaşlarının 152 over kanseri nedeniyle takipli hastada yaptığı çalışmada; BEERS kriterlerine göre uygunsuz ilaç kullanımı, bizim çalışmamıza benzer şekilde %35 oranında görülmüştür. Ancak bu çalışmada polifarmasi toplam sağ kalım için bir prediktör olarak belirlenememiştir (15).

1213 rekürren over kanserinin dahil edildiği bir çalışmada polifarmasi hematolojik evre III/IV toksisiteyle ilişkili bulunmuş ancak toplam sağ kalım ile arasındaki ilişki gösterilememiştir (16). 3795 epitelyal over kanserinin dahil edildiği bir çalışmada polifarmasi ve uygunsuz ilaç kullanımı mortalitede artış ile ilişkili bulunmuştur (17). 718 hastanın dahil edildiği ve %6 sının jinekolojik kanser olduğu bir çalışmada polifarmasi %61.3, potansiyel uygunsuz ilaç kullanımı ise %67.1 oranında bulunmuştur. Polifarmasi olanlar daha yaşlı, daha fazla ko-morbiditesi olan, fonksiyonel ve fiziksel olarak daha bağımlı hastalar olarak belirlenmiştir (18).

Çalışmamızın güçlü yönleri, jinekolojik kanserler nedeniyle opere olup ve sonrasındaki yoğun bakım yatış süresiyle polifarmasi arasındaki ilişkinin değerlendirildiği ilk çalışma olmasıdır. Bunun yanında sadece ilaç sayısı değil Türkiye'ye özgü TIME kriterleri ile uygunsuz ilaç kullanımın değerlendirilmiş olması önemlidir. Çalışmamızın tek merkezde ve retrospektif dizaynlı olması; ayrıca sadece reçeteli ilaçlarının değerlendirilmiş; tezgah üstü ilaçların (Over The Counter, OTC) değerlendirilememiş olması kısıtlılıklar arasındadır. Yoğun bakım yatış süresini etkileyen diğer faktörlerden mekanik ventilatör uygulanıp uygulanmaması, inotroperatif ajan ihtiyacının olup olmadığının belirlenememiş olması çalışmanın diğer kısıtlılıklarıdır.

Sonuç olarak jinekolojik kanserler nedeniyle opere edilen ve post operatif dönemde yoğun bakımda takip edilen hastalarda, polifarmasi yatış süresiyle ilişkilidir. Hastaların yoğun bakım kalış sürelerini ön görmek için her hastada, hastaların yatış öncesi ko-morbiditeleri ve ilaç kullanımlarını değerlendirmek anahtar noktalardan biridir.

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Second-Third Trimester Aspartate Aminotransferase to Platelet Ratio Index in Predicting in Intrahepatic Cholestasis of Pregnancy and its Relationship with Neoanatal Intensive Care Unit Requirement: A Case Control Study From a Tertiary Hospital

İkinci-Üçüncü Trimesterde Aspartat Aminotransferaz Trombosit Oranı İndeksinin Gebeliğin İntrahepatik Kolestazı Öngörmesi ve İndeksin Yenidoğan Yoğun Bakım Gereksinimi ile İlişkisi: Üçüncü Basamak Bir Hastaneden Vaka Kontrol Çalışması

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ÖZ

Amaç: Gebeliğin ikinci-üçüncü trimesterinde intrahepatik kolestaz (ICP) öngörüsünde aspartat aminotransferaz trombosit oranı indeksi (APRI) skorunu değerlendirmek.

Gereçler ve Yöntem: Bu çalışmaya 2021-2022 yılları arasında hastanemiz Perinatoloji kliniğinde değerlendirilen İCP tanılı hasta grubu (n=40) ve kontrol grubu (n=70) dahil edildi. Her iki grubun laboratuvar testleri retrospektif olarak incelendi. İki grup arasında yaş, gravida, parite, vücut kitle indeksi, üçüncü trimester laboratuvar testleri ve birinci trimester aspartat aminotransferaz (AST)/trombosit sayısı [AST - trombosit oran indeksi (APRI) skoru] skorları karşılaştırıldı. Çalışma grubunda APRI skor indeksi ile neonatal sonuçlar arasındaki ilişki değerlendirildi. Çalışmada gebelerde ikinci-üçüncü trimesterde ICP'yi öngörmede APRI skorunun cut-off değeri belirlendi.

Bulgular: ICP'li hastalarda kontrol grubu ile karşılaştırıldığında anlamlı olarak daha yüksek APRI skorları vardı (p <0.001). ROC analizinde, APRI skorunun ikinci-üçüncü trimesterde ICP'yi öngörme kesme değeri, %78 duyarlılık ve %79 özgüllük ile 0,092 idi. Spearman korelasyonu, çalışma grubunda APRI skoru ile yenidoğan yoğun bakım ünitesi (YYBÜ) gereksinimi arasında anlamlı pozitif bir ilişki olduğunu gösterdi (p=0.022). Hastaların demografik özellikleri benzerdi.

Sonuç: APRİ skoru,gebeliğin intrahepatik kolestazında ve YYBÜ gereksiniminin tahmininde tatmin edici duyarlılık ve özgüllük ile kullanılabilir.Gebeliğin intrahepatik kolestazı olumsuz perinatal sonuçlarla ilişkili olduğundan, bu indeks klinik uygulamalarda daha olumlu sonuçlar elde etmeleri için hekimlere yardımcı olabilir.

Anahtar Kelimeler: Gebelikte intrahepatik kolestaz, APRI skoru, serum açlık safra asidi, YYBÜ gereksinimi

ABSTRACT

Aim: To evaluate the aspartate aminotransferase platelet ratio index (APRI) score in the prediction of intrahepatic cholestasis (ICP) in the second-third trimester of pregnancy.

Material and Methods: The patient group (n=40) and control group (n=70) diagnosed with ICP who applied to the hospital Perinatology clinic between 2021-2022 were included in this study. Laboratory tests of both groups were analyzed retrospectively. Age, gravida, parity, body mass index, third trimester laboratory tests and first trimester aspartate aminotransferase (AST)/platelet count ratio [AST - platelet ratio index (APRI) score] APRI scores were compared between the two groups. The relationship between APRI score index and neonatal outcomes was evaluated in the study group. In the study, the cut-off value of the APRI score was determined for predicting ICP in second-third trimester in pregnant women.

Results: Patients with ICP had significantly higher APRI scores compared with controls (p <0.001). In the ROC analysis, the cut-off value for APRI score to predicting ICP in second-third trimester was 0.092 with 78 % sensitivity and 79 % specificity. Spearman's correlation indicated that there was a significant positive association between APRI score and neonatal intensive care unit (NICU) requirement in the study group (p=0.022). The demographic characteristics of patients did not differ, except for aspartateamino transferase and alanine transferase values.

Conclusions: APRI score may be used in the prediction of ICP development and NICU requirement with satisfactory sensitivity and specifity. As ICP is associated with poor perinatal outcomes, this novel index may help physicians in their clinical practice to obtain more favorable outcomes.

Keywords: Intrahepatic cholestasis in pregnancy, APRI score, Serum fasting bile acid, NICU requirement

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease that is characterized by elevated serum aminotransferase levels, usually presents in the form of itching and high bile acid levels, develop during the second or third trimester of pregnancy. ICP resolves spontaneously within a few weeks after delivery (1, 2). It increases the risk of perinatal complications, including preterm delivery (spontaneous or iatrogenic), neonatal respiratory distress syndrome, fetal distress,meconium dyeining of the amniotic fluid and increased risk of intrauterine fetal death (3, 4).

Aspartate aminotransferase (AST) - platelet ratio index (APRI) has been used in many studies to diagnose liver injury(5). Although the APRI score has been found to be a reliable predictor of fibrosis in previous studies(6), it remains unclear whether it is also a strong predictor for ICP.

In this study aimed to evaluate whether the APRI score can be used to predict ICP in the second or third trimester and whether there is a correlation between neonatal intensive care unit (NICU) requirement and APRI scores in the study group.

MATERIALS AND METHODS

Clinical data for patients who presented to the Turkish Ministry of Health Ankara City Hospital at the Perinatology Clinic with ICP between 2020 and 2022 were evaluated retrospectively. The present study protocol was approved by the institutional ethics committee in suitability with the principles of the Declaration of Helsinki and approved by Ankara City Hospital Clinical Ethics Committee no:2 (date:07/12/2022, number:E2-22-2942).

A diagnosis of ICP was made,in cases with unexplained, generalized pruritus ,abnormal liver function tests [serum AST and ALT(alanine aminotransferase) >40 U/l] and fasting serum bile acid level above 10 mmol/l in pregnant women in the second or third trimester(7). While evaluating all the cases, abdominal and hepatobiliary ultrasonographic imaging findings were within normal limits and viral hepatitis serology negative for hepatitis. Pregnants with systemic diseases, such as diabetes, hypertension, and kidney disease, smokers, women with multiple pregnancies, and pregnant women with fetal anomalies were excluded from the study. Fetal biometry, gestational week, gestational age at birth, fetal birth weight, platelet counts, second or third trimester fasting bile acid levels, and APRI score were collected.Parameters were compared between the two groups.Apgar scores (first-fifth minute), and neonatal intensive care requirement were also noted.

Statistical analysis

In the analysis performed with Clincalc, the power was 95% and p value of 0.05, the total sample was 70, with at least 35 patients in the case and control groups(8). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 22, IBM, SPSS for Windows, NY: IBM Corp.).Descriptive statistics were presented as median and interquartile range nonnormally distributed variables. Median values were compared by Mann–Whitney U-test for nonnormally data and student T-test. Sperman's correlation analysis was performed between APRI score and NICU requirement in the study group. Finally, the receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value of the APRI level for predicting ICP in the second-third trimester.P value <0.05 was regarded as statistically significant.

RESULTS

The study included a total of 110 pregnant women (18-44 years), of whom 40 had ICP and 70 were healthy controls. There was no statistically significant difference between the two groups in terms of maternal age, mean gestational week,fetal birth weight,gravidity,parity, BMI(body mass index),PLT count (platelet), first-five minute Apgar score (p > 0.05) Table 1.

Table 1: Maternal Demographic and laboratory Parameters and Neonatal Outcomes

Variable	Study group (n = 40)	Control group (n=70)	p value
Maternal age(year) (median, IQR)	32(5)	31(7)	0.093
Gravidity (median, IQR)	2(2)	2(2)	0.261
Parity (median, IQR)	1(2)	1(1)	0.096
BMI(kg/m^2)	26(6)	27(8)	0.230
APRI score	.251(.32)	.067(.04)	0.000*
AST(U/L)	55(75)	17(8)	0.000*
ALT(U/L)	71(128)	15(11)	0.000*
PLT(10^6/µL)	246±51	267±66	0.091
Gestational week(week)	33(3)	34(6)	0.112
Gestational week at birth(week)	37(2)	38(3)	0.007*
Fetal birth weight(gr)	2760(628)	3032(660)	0.229
Apgar 1st minute (median, IQR)	7(1)	7(1)	0.984
Apgar 5th minute (median, IQR)	9(1)	9(1)	0.885
NICU (n, %)	24(60 %)	9(12.5 %)	0.000*

Note: Data given as median and interquartile range

Abbreviations:BMI;body mass index,APRI;aspartate aminotransferase to platelet ratio index,AST; aspartate aminotransferase,ALT;alanine aminotransferase,PLT;platelet,n;number,IQR;interquartile range.

Neonatal intensive care unit requirement,AST,ALT levels and APRI score index were statistically significantly higher (p < 0.001) compared to the control group Table 1. A statistically significant positive correlation was found between APRI scores and NICU need in pregnant women with ICP(p=0.022) Table 2.

Table 2: Correlations of APRI Value in Newborns with and without NICU Requirement in the Study Group

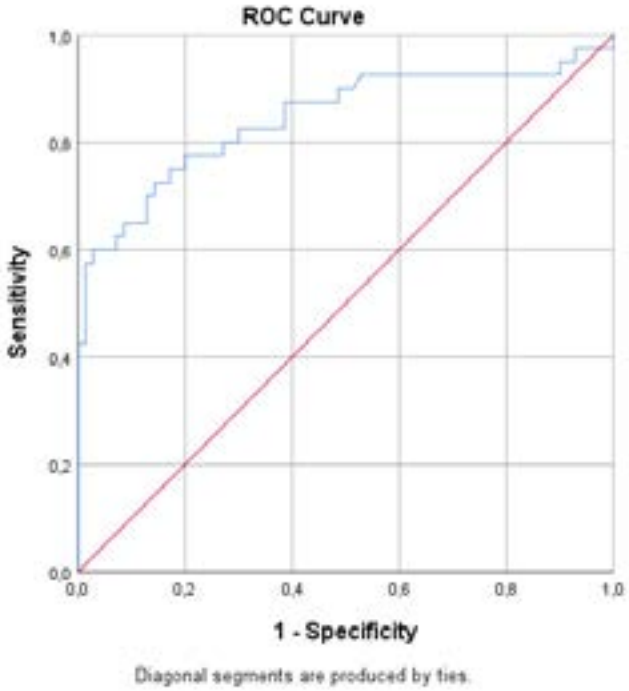
Study group	NICU requirement		*p* value
	Present (n = 24)	Absent (n = 16)	
APRI	.315 (1.21)	.107 (.701)	0.022*

Note: Data given as median and interquartile range

Abbreviations: APRI; aspartate aminotransferase to platelet ratio index, NICU; neonatal intensive care unit.

According to the ROC analysis, the optimal cut-off value of APRI level for predicting ICP in the second-third trimester was calculated as 0.092, with 78% sensitivity and 79% specificity (AUC: 0.844, 95% CI: .757-.932, p< 0.000) Figure 1

Figure 1: Receiver Operating Characteristic Curve Analysis to Assess the Performance of APRI in Predicting ICP in the Second-Third Trimester



DISCUSSION

In this study, we investigated the maternal APRI scores of a group of pregnant women with ICP and compared their results with a control group with healthy pregnancies. We found that when compared to the healthy control group, the APRI scores were statistically significantly higher in the patients with ICP, which develops on an inflammatory basis and is the most common liver disease in pregnancy.

ICP complicates approximately 0.35–0.65% of pregnancies worldwide (9).Although the etiology of ICP is not yet fully understood, many factors such as environmental effects, ethnic,genetic and familial factors, geographic variations, the activation of inflammatory cells, hormonal factors and placental pathologies may contribute to its pathogenesis (10, 11).Prediction and prevention of pregnancy-related complications are of great importance (12). It is known that there is an increased risk of preterm birth, increased need for NICU and stillbirth in ICP pregnancies, and these conditions increase as maternal acid level increases (13). Although the number of studies on early estimation of ICP has increased recently in the literature, previous studies have generally focused on adversefetal and maternal outcomes. In our study, the need for NICU was found to be statistically higher in the ICP group, which is expected in newborns of pregnant women with cholestasis. However,no difference was found between the groups in terms of APGAR scores.Numerous algorithms and guidelines focused on the management of risk factors in ICP have been proposed, and early diagnosis, treatment, and observation may help reduce fetal and maternal complication rates(14, 15). Hepatic transaminases were elevated in most of the ICP patients(16, 17), and AST and ALT levels, which are hepatic transaminases, were higher in our study.

The APRI score is determined by dividing the AST level from blood tests by the platelet count.Score has previously been used as a prognostic factor for predicting HELLP syndrome and for pregnancy outcomes in women with chronic liver disease(18, 19). Fetal and maternal complications can be reduced by early diagnosis and treatment of ICP. Tolunay et al. found a significant positive correlation between fasting bile acid levels and first trimester APRI score in women with ICP and determined a cut-off value for the APRI score with high sensitivity and specificity to predict ICP in the first trimester (20). In another previous study, patients with ICP had significantly higher first trimester APRI scores and lower first trimester AST/ALT ratio than healthy controls(21). Studies have shown that ICP is an inflammatory process and there is a relationship between inflammation markers and the severity of the disease(22). In liver biopsies of women with ICP, pathological findings such as biliary plugs containing hepatocytes and canaliculi without dilatation or injury, centrilobular cholestasis, suggesting that ICP is a reversible disease were detected.(22, 23).

In this study, we hypothesized that the APRI score might be useful and effective in diagnosing ICP in the second/third trimester. As APRI reflects both liver function and inflammation, this novel index may indicate ICP earlier than the clinical findings. Moreover, it can give the physicians an opinion about the severity of ICP and related neonatal morbidity. We tried to determine a cut-off value by using the APRI score in patients with ICP and also investigated the existence of a correlation between APRI score and NICU need in pregnant women with cholestasis.

The gold standard for the diagnosis of ICP is serum fasting bile acid level. However, measurement of fasting serum bile acid levels is not performed in all institutions, and there is a relatively long turnaround time in institutions that do. Therefore, alternative indexes, especially those that are easy to access, less costly, and facilitate the timely evaluation of tests performed in almost every healthcare facility for ICP may have significant clinical value.

We think that this study investigating the value of the second-third trimester APRI score in pregnant women with cholestasis will be beneficial to the clinical situation and our results will contribute to the literature. However, the relatively small number of patients and the lack of perinatal long-term results are the main limitations of this study. In this context, multicenter randomized controlled studies with a large number of participants are needed.

CONCLUSION

We found statistically higher NICU requirement in newborn of patients with high APRI scores in patients with ICP. APRI score may be used in the prediction of ICP development and NICU requirement with satisfactory sensitivity and specifity. As ICP is associated with poor perinatal outcomes, this novel index may help physicians in their clinical practice to obtain more favorable outcomes. Consequently, our data highlighted effective,useful the role of APRI score as a reliable predictor easy to use for to predicting ICP in the second-third trimester.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Çok Düşük Doğum Ağırlıklı Preeklamptik Anne Bebeklerinin Erken ve Geç Dönem Sonuçlarının Değerlendirilmesi

Evaluation of Early and Late Term Outcomes of in Very Low Birth Weights Infants With Maternal Preeclampsia

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ÖZ

Amaç: Preeklampsi hem maternal hem de neonatal komplikasyonlarla seyreden oldukça yaygın bir gebelik komplikasyonudur. Preeklampsi ile prematürelik ve prematüre bebeklerde morbidite oranları artmaktadır. Bu çalışmada çok düşük doğum ağırlıklı bebeklerde preeklampsinin erken ve geç dönem morbiditeler üzerine etkisini araştırmayı amaçladık

Metod: Çalışmaya Ocak2010-Aralık2013 tarihleri arasında yenidoğan yoğun bakım ünitemizde (YYBÜ) yatarak tedavi gören <34 gestasyon haftası olan bebeklerin dosyaları geriye dönük olarak incelendi. Annelerinde preeklampsi olan ve olmayan bebeklerin demografik verileri ve neonatal morbiditeleri karşılaştırıldı.

Bulgular: Çalışmaya toplam 669 hasta dahil edildi. 191 hastanın (%28,5) annesinde preeklampsi (grup1) vardı. 478 hasta (grup2) kontrol grubu olarak değerlendirildi. Her iki grubun demografik verileri benzerdi. Sezeryan doğum oranı grup 1'de anlamlı olarak daha yüksek bulundu. Her iki grup arasında intrauterin büyüme kısıtlılığı (İUBK) açısından fark bulunmazken, grup 1'de SGA görülme oranı daha yüksekti. Solunumsal morbiditelere bakıldığında grup 1'de RDS görülme oranı daha yüksek bulundu. Gruplar arası orta-ağır BPD gelişimi açısından fark görülmedi. Evre 3-4 intrakraniyal kanama ve patent duktus arteriozus oranları her iki grupta benzerdi. Gruplar arası evre 2-3 NEK ve beslenme intoleransı açısından fark yoktu. Mortalite oranları gruplar arası benzer bulundu.

Sonuç: Çalışmamızın verilerine göre preeklamptik anne bebeklerinde solunumsal morbiditeler daha sık görülmektedir. Aynı zamanda bu bebeklerde SGA görülme oranı da daha yüksektir.

Anahtar kelimeler: preeklampsi, prematüre, RDS, SGA

ABSTRACT

Objective: Preeclampsia is a common pregnancy complication that is associated with both maternal and neonatal complications. Preeclampsia is known to increase the rates of prematurity and morbidity in premature infants. The aim of this study was to investigate the impact of preeclampsia on early and late-term morbidities in very low birth weight infants.

Study Design: The medical records of infants born at <34 gestational weeks who were admitted to our neonatal intensive care unit (NICU) between January 2010 and December 2013 were retrospectively reviewed. The demographic data and neonatal morbidities of infants born to mothers with and without preeclampsia were compared.

Results: A total of 669 patients were included in the study. 191 patients (28.5%) had mothers with preeclampsia (group 1). 478 patients (group 2) were considered as the control group. The demographic data of both groups were similar. The rate of cesarean section was significantly higher in group 1. There was no significant difference in terms of intrauterine growth restriction (IUGR) between the two groups, but the rate of small for gestational age (SGA) was higher in group 1. When respiratory morbidities were examined, the rate of respiratory distress syndrome (RDS) was found to be higher in group 1. There was no difference between the groups in terms of moderate-severe bronchopulmonary dysplasia (BPD) development. The rates of stage 3-4 intracranial hemorrhage and patent ductus arteriosus were similar in both groups. There was no difference between the groups in terms of stage 2-3 necrotising enterocolotis (NEC) and feeding intolerance. The mortality rates were similar between the groups.

Conclusion: According to our study data, respiratory morbidities are more frequently observed in infants of preeclamptic mothers. Additionally, the rate of small for gestational age (SGA) is higher in these infants.

Key words: preeclampsia, preterm, RDS, SGA

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GİRİŞ

Preeklampsi (PE) hem maternal hem de neonatal komplikasyonlarla seyreden oldukça yaygın bir gebelik komplikasyonudur. Tüm gebeliklerin yaklaşık %3-5 inde görülür (1). Preeklampsi 20. Gebelik haftasından sonra annede yaygın endotel bozukluğu ile karakterize proteinüri ve 140/90 mmhg veya daha yüksek kan basıncı ile giden hipertansif bir hastalıktır (2).Maternal kan basıncının 160/110 mmHg ve üzerinde olduğu durumlarda ağır PE tanısı koyulur (3).

Gebelik haftası 34 haftadan önce görülen PE de doğum hemen gerçekleştirilerek maternal komplikasyonlar önlenmeye çalışılsa da neonatal mortalite ve morbidite artmaktadır (4,5).

Prematür doğumların yaklaşık %20 si, IUBK nın %12 si maternal preeklampsi nedeniyle gerçekleşmektedir (6). Preeklamptik anneden doğan bebeklerde intaventriküler kanama (İVK), respiratuvar distres sendromu (RDS), nekrotizan enterokolit (NEK), prematüre retinopatisi (ROP) gibi birçok morbiditeler sağlıklı popülasyona göre daha sık görülebilir (6,7).

Bu çalışmada 34 gebelik haftasından önce PE tanısı alan annelerin bebekleri ile maternal risk faktörü olmayan bebeklerin morbiditelerini karşılaştırmayı amaçladık.

MATERYAL VE METOD

Retrospektif çalışmamıza Ocak 2010-Aralık 2013 tarihleri arasında yenidoğan yoğun bakım ünitemizde (YYBÜ) yatarak tedavi gören gestasyon haftası <34 hf altında olan bebekler dahil edildi. Hastanemiz etik kurulundan çalışma için onay alındı (24/2018). Hastalar 2008 Helsinki bildirgesine uygun olarak çalışmaya dahil edildi. Major konjenital anomalisi olan, annenin veya bebeğin klinik bilgileri eksik olan hastalar çalışma dışı bırakıldı. Bebeklerin aile öyküsü, demografik özellikleri, perinatal risk etmenleri, morbiditeleri hasta dosyaları incelenerek kaydedildi. Gebelik haftası son adet tarihi ve modifiye Ballard skorlaması baz alınarak kaydedildi. Doğum ağırlığı 10-90 persantil (p) arasında olan bebekler haftasına uygun doğum ağırlıklı (AGA), 10 p altında olanlar ise haftasına göre düşük doğum ağırlıklı (SGA), 90 p üzerinde olanlar iri bebek (LGA) olarak kaydedildi.

Respiratuvar distres sendromu tanısı hastanın klinik bulguları, oksijen ihtiyacı postero-anterior akciğer grafi bulguları değerlendirilerek koyuldu (8). Hastaların birinci haftasındaki transkraniyal ultrasonografi (USG) bulguları kaydedildi. Kraniyal kanama derecesi Papile sınıflamasına göre yapıldı (9). Nekrotizan enterokolit sınıflaması modifiye Bell skorlaması kullanılarak yapıldı (10). Bronkopulmoner displazi (BPD) tanımı olarak postnatal 36. Gestasyon haftasında oksijen ihtiyacının devam etmesi olarak kabul edildi (11). Çalışmanın yapıldığı yıllar arasında kadın doğum kliniğimizde gebelik hipertansiyonu ACOG sınıflamasına göre yapıldı (12).

İstatiksel analiz

Tüm istatiksel veriler IBM SPSS programı üzerinde yapıldı. Normal dağılım gösteren değişkenler bağımsız t-test ile, oranlar ve kategorik değişkenler ki kare testi ile karşılaştırıldı. $p<0.05$ istatiksel olarak anlamlı kabul edildi.

BULGULAR

Ocak 2010-Aralık 2013 tarihleri arasında verilerine ulaşılan gebelik haftası 34 haftanın altında olup YYBÜ'ye yatan 690 hastadan, 10 bebek anne verileri eksik olduğu için, 5 bebek majör konjenital anomali nedeniyle, 6 bebek hasta verileri yetersiz olduğu için çalışma dışı bırakıldı. Çalışmaya toplam 669 hasta dahil edildi. Preeklamptik anneden doğan 191 hasta (%28.5) grup 1, annesinde preeklampsi olmayan 478 (%71.5) hasta grup 2 olarak değerlendirildi. Her iki grubun demografik verileri tablo 1 de özetlenmiştir.

Tablo 1. Preeklamptik anne bebeği olan ve olmayan hastaların demografik verilerinin karşılaştırılması

	Grup 1 (n:191)	**Grup 2 (n:478)**	**p değeri**
Erkek cins (n,%)	93 (48.7)	233(48.8)	0.80
Doğum haftası, hafta, (mean±SD)	28.9 ± 2.09	28.5 ± 1.9	0.09
Doğum ağırlığı,gr (mean±SD)	986.39 ± 194.93	1031.45 ± 190.63	0.07
C/S ile doğum (n,%)	181 (95.3)	375 (78.5)	**<0.01**
Anne yaşı (mean±SD)	29.8 ± 6.2	27.5 ± 5.8	**<0.01**
IUBK (n,%)	43(27.9)	63(17)	0.06
SGA (n,%)	90 (47.1)	190 (39.7)	**<0.01**
Apgar 5. Dk (median, min-max)	8 (2-9)	8(3-9)	0.353
Antenatal steroid (n,%)	65(34)	163(34.1)	0.97
Plasenta anomalisi (n,%)	7(3.8)	17(3.7)	1.00
Gestasyonel diyabet (n,%)	7(3.7)	14(2.9)	0.62
Çoğul gebelik (n,%)	21(10.9)	52(10.8)	1.00
Mortalite (n,%)	37 (19.5)	108 (23.1)	0.351

Ortalama gebelik haftaları, doğum ağırlıkları ve cinsiyetleri her iki grupta benzer bulundu. Aynı zamanda 5. dk APGAR skorları, antenatal steroid uygulaması arasında da fark yoktu. Grup 1 de anne yaşı (29.8 ± 6.2 ve 27.5 ± 5.8), sezeryan doğum oranı (181(%95.3) ve 375 (%78.5) ve SGA görülme oranı (90(%47.1) ve 190(%39.7)) diğer gruba göre anlamlı yüksek bulundu ($p<0.05$). İntrauterin büyüme kısıtlılığı (IUBK) her iki grupta benzerdi. Plasenta anomalisi, gestasyonel diyabet, çoğul gebelik oranları benzerdi. Mortalite oranları arasında gruplar arası anlamlı fark yoktu (Tablo 1).

Hastaların morbiditeleri ve tedavileri tablo 2 de özetlenmiştir.

Tablo 2. Gruplar arası tedavi ve morbiditelerin karşılaştırılması

	Grup 1 (n: 191)	**Grup 2 (n: 478)**	**p değeri**
RDS (n,%)	129 (67.5)	273 (57.2)	**0.014**
Surfaktan uygulaması (n,%)	116 (60.7)	242 (50.8)	**0.025**
BPD (n,%)	14(8.9)	51 (10.6)	0.08
PDA (n,%)	76 (42.5)	162 (37.5)	0.274
İKK (evre 3-4) (n,%)	12 (8.5)	43 (12.6)	0.212
NEK(evre 2-3**)** (n,%)	11 (6.3)	23 (5.5)	0.7
ROP (n,%)	77 (49)	177 (49)	1.0
Beslenme intoleransı (n,%)	89(50.9)	211(51.2)	1.0
Tam enteral beslenmeye geçiş (gün, mean±SD)	18± 1	17.5±10	1.0
Taburcu gün(gün,mean±SD)	58.9±23.3	58±24.7	0.71

RDS: Respiratuvar distres sendromu, **BPD:** Bronkopulmoner displazi, **PDA:** Patent duktus arteriyozus, **İKK:** İntrakraniyal kanama, **NEK:** Nekrotizan enterokolit, **ROP:** Prematüre retinopatisi

Surfaktan uygulaması (%60.7 ve %50.8 p<0.05) ve RDS görülme oranı (%67.5 ve %57.2 p<0.05) Grup 1 de anlamlı yüksek bulunurken, BPD oranları gruplar arası benzerdi. Patent duktus arteriozus tanısı nedeniyle tedavisi alma, ileri evre İKK gelişme, beslenme intoleransı görülme, tam enteral beslenmeye geçiş günü ve evre 2-3 NEK gelişmesi açısından her iki grup arasında anlamlı farklılık bulunmadı. Hastaların ortalama taburcu günleri arasında da istatiksel farklılık görülmedi.

TARTIŞMA

Çalışmamızın sonucunda preeklamptik anneden doğan bebeklerde RDS sıklığı ve surfaktan ihtiyacı preeklamptik olmayan anne bebeklerine göre daha fazla bulunmuştur.

Preeklampsi en sık görülen gebelik komplikasyonlarından biridir (1). Preeklamptik anne bebeklerinde prematürelik, asfiksi, fetal büyüme geriliği ve ölüme kadar gidebilen birçok klinik bulgu görülebilmektedir (13).

Preeklampsinin prematüre bebeklerde solunum sıkıntısını arttırdığı bilinmektedir (5,6). Jelin ve ark nın yaptığı retropektif bir çalışmada gebelik haftası 30 hafta altındaki bebeklerde RDS sıklığının preklamptik anne bebeklerinde anlamlı olarak daha yüksek olduğunu görmüşlerdir (14). Aynı şekilde bu bebeklerde SGA görülme oranının anlamlı olarak daha yüksek olduğunu bulmuşlardır (14). Bizim çalışmamızda preeklamptik anneden doğan bebeklerde RDS sıklığı ve surfaktan ihtiyacı preeklamptik olmayan anne bebeklerine göre daha fazla bulunmuştur. Gebelik haftası 34 hafta altı bebeklerde benzer sonuçlar elde edilmiştir. Chang ve ark ı da gebelik haftası 32 haftanın altında doğan preeklamptik anne bebeklerinde RDS sıklığının iki katı arttığını göstererek bunu uteroplasental yetersizliğin yarattığı hipoksinin surfaktan yapımını baskıladığını ve eskiden bilinenin aksine preeklampsinin fetal akciğer olgunlaşmasını hızlandırmadığı sonucuna ulaşmışlardır (15). Bizim çalışmamızda da preeklamptik bebeklerin %60.7 sinin surfaktan ihtiyacı olmuştur.

Preeklampside en sık görülen neonatal sonuçlar intrauterin büyüme kısıtlılığı ve SGA dır (14,16). Çalışmamızda intrauterin büyüme geriliği PE olan grupta daha sık görülmesine rağmen istatiksel olarak anlamlı bulunmadı. Çalışmaya alınan hastaların doğum haftalarının daha küçük olması, yakın obstetrik takip ve intrauterin kötü koşullara fazla maruz kalmadan doğumun gerçekleştirilmesinde bunun etkili olduğunu düşünmekteyiz. Buna rağmen SGA görülme oranı PE olan grupta anlamlı olarak yüksekti. Preeklampsi ile komplike gebeliklerden doğan bebeklerin komplikasyonsuz gebeliklerden doğan bebeklere göre %5 oranında daha düşük doğum ağırlığı ile doğduğu belirtilmektedir ve bu fark PE ne kadar erken gebelik haftasında başlarsa o kadar artmaktadır (17,18).

Erken veya geç maternal yaşın preterm doğum, düşük doğum ağırlığı ve SGA riskini arttırdığı uzun zamandır bilinmektedir (19,20). Yaşla birlikte gelişen fizyolojik ve fiziksel değişiklikler hastalıkların riskini arttıran etmenlerden biridir (21). Maternal yaş ve PE arasındaki ilişkiyi araştıran çalışmalarda vardır. Lamminpää R ve ark nın yaptığı bir çalışmada 35 yaş üstü gebeliklerde PE riski 35 yaş altı gebeliklere göre 1.5 kat artmış olduğu belirtilmiştir (22). Li X ve ark nın yaptığı başka bir çalışmada da erken başlangıçlı PE de 35 yaş üstünün aşırı preterm doğum için risk olduğunu ve erken gebelik yaşının ise düşük doğum ağırlığı ve SGA ile ilişkili olduğunu belirtmişlerdir (23). Bizim çalışmamızda da kontrol grubuna göre PE görülen hastaların maternal yaşı istatiksel olarak daha yüksek bulundu. Çalışmamız sonuçlarına göre maternal yaş için bir sınır belirtmek istatiksel olarak mümkün değildir. Literatürdeki yapılan çalışmaları baz alarak gebelik yaşının maternal ve fetal komplikasyonları etkilediğini söyleyebiliriz (19-23).

Çalışmamızda neonatal morbiditeler üzerinde erken dönemde görülen solunum sıkıntısı dışında gruplar arası diğer morbiditelerde farklılık bulunmamıştır. Hansen ve ark nın yaptığı bir çalışmada PE nin patofizyolojisinde rol oynadığı düşünülen antianjiogeneze bağlı düşük VEGF düzeylerinin BPD riskini 3 kata kadar arttırdığını belirtmişlerdir (24).

Çalışmamızda gruplar arası BPD gelişiminde fark bulunmadı. Bu sonucu PE nin derecesinin, klinik uygulama ve bakım farklılığından kaynaklandığını düşünmekteyiz. Hem bizim çalışmamızda hem de literatürde birçok çalışma da PE şiddeti ve başlangıç zamanı çalışmalarda belirtilmemiş. Literatürdeki sonuçların farklılığının büyük oranda bunun ile ilgili olduğunu düşünmekteyiz. Çalışmamızda ortalama doğum haftası 28.9 dur. Bu hastaların erken doğum nedeninin ileri derecede preeklampsi olduğunu düşünmekteyiz. Gruplar arası demografik verilerde fark olmadığı için çoklu istatistiksel verileri karşılaştırmadık. Çalışmamızın kısıtlılıkları; retrospektif bir çalışma olması, preeklampisinin başlangıç zamanının net olmaması gösterilebilir. PE nin fetus ve yenidoğan üzerine etkilerini anlayabilmek için daha geniş prospektif çalışmalara ihtiyaç vardır.

SONUÇ

Çok düşük doğum ağırlıklı preeklamptik anne bebeklerin de solunumsal morbiditeler daha sık görülmektedir. Aynı zamanda bu bebeklerde SGA görülme oranı da daha yüksektir. Pre-

eklamptik anne bebeklerinin uygun koşulların sağlanabileceği yenidoğan yoğun bakım ünitelerinin bulunduğu merkezlerde doğması ve multidisipliner yaklaşımın bu bebeklerde morbidite ve mortaliteyi azaltacağını düşünmekteyiz.

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Özgün Araştırma / Original Article

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Extrauterine Malignancies Detected on Papanicolaou Smear: The Clinical and Cytomorphological features of Eight Patients

Papanicolaou Smear'da Saptanan Rahim Dışı Maligniteler: Sekiz Hastanın Klinik ve Sitomorfolojik Özellikleri

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ÖZ

Amaç: Papanicolau smear (Pap), serviks kanseri tanısında etkili bir tekniktir. Bu muayenede atipik glandüler hücreler ortaya çıkabilir ve bazen ekstratuerin malignitenin ilk belirtisi olabilir. Bu çalışmada sunulan 8 vaka, tümü klasik Pap smear'larda tespit edilen, daha önce bilinmeyen ekstrauterin tümörlerin nadir görülen vakalarıdır

Metod: Klinik veri tabanının retrospektif analizi ile, standart Pap smear'da daha önce teşhis edilmemişrahim dışı tümörlerin bulunması amacıyla sitoloji arşivi ve hasta dosyaları taraması yapıldı.Taramada sekiz hasta bu kriterlerde bulundu. Bu hastaların hücre blokları ve sitomorfolojik incelemeleri tekraralanarak beraberinde klinik veriler incelendi.Bulgular: Pap smear tüm olgularda malignitenin ilk bulgusuydu. Hastalar asemptomatikti veya spesifik olmayan semptomları vardı. Kesin tanı yeterli radyolojik tetkik ve biyopsi sonrası konuldu. Sekiz vakanın tümü, histolojik olarak kanıtlanmış bir primer tümörün benzer sitomorfolojik özelliklerine sahipti. Atipik glandüler hücre grupları altı hastada en dikkat çekici bulguydu. Diğer iki hastada lenfatik kökenli hücreler ve atipik lenfositler saptandı. İmmünohistokimya ile hücre bloğu, üç vakada tanıyı net olarak doğruladı.

Sonuç: Pap smear kanser taraması için dünya çapında kabul gören bir yöntemdir. Rahim ağzı kanserleri için yüksek özgüllük ve duyarlılığa sahip olmasına rağmen, bu çalışmanın sonuçları, rutin taramalarda alınan Pap smear'ların titiz bir şekilde incelenmesinin asemptomatik hastalarda rahim dışı kanserleri de saptayabileceğini vurgulamaktadır.

Anahtar kelimeler: Papanicolaou Smear, Asemptomatik tarama, Malignite

ABSTRACT

Objective: Papanicolau smear (Pap) is an effective technique for the diagnosis of cervix cancer. Atypical glandular cells may be revealed in this examination and occasionally may be the first sign of extratuerine malignancy. The 8 cases presented in this study are uncommon cases of previously unknown extrauterine tumors all detected on classical Pap smears.

Study Design: A retrospective analysis of the clinical database identified eight women with previously undiagnosed extrauterine tumor detected on standard Pap smear. Clinical data were obtained from patient files and microscopic examination was repeated on the material obtained from the cytology archives. Cellblock and cytomorphology examinations were made, and clinical data were reviewed together with histopathology.

Results: Pap smear was the first sign of malignancy in all cases. The patients were asymptomatic or had non-specific symptoms. Definitive diagnosis was made after adequate radiological work up and biopsy. All eight cases had similar cytomorphological features of a histologically proven primary tumor. Atypical glandular cell groups were the most remarkable sign in six patients. In the other two patients, cells of lymphatic origin and atypical lymphocytes were detected. Cellblock with immunohistochemistry confirmed the diagnosis in three cases.

Conclusion: Pap smear is a worldwide accepted method for cancer screening. Although it has high specificity and sensitivity for cervical cancers, the results of this study highlight that rigorous examination of Pap smear.

Key words: Papanicolau smear, Malignancies, Asymptomatic screening

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INTRODUCTION

The Pap smear test was originally designed to detect premalignant cervical lesions and cancer, based on cytological examination of vaginal smear, and this test remains the gold standard as a low-cost, universal screening modality, especially in low-resource environments (1,2). Exfoliative cytology may also indicate the presence of malignancies other than cervical cancer(3). Malignant cells from extrauterine cancers can come from direct extension to the cervix or vagina in patients with known malignancies(4).

In very rare cases, atypical or malignant cells detected in a cervical smear can be the first manifestation of extrauterine malignancy (3). The most common primary sites being the ovaries, followed by the gastrointestinal tract, fallopian tubes and breasts (5). Data in literature demonstrate that extrauterine cancer detected from a Pap smear is very rare (2). However, advances in the smear examination techniques such as liquid-based cytology, molecular-based HPV genotyping, and analysis of immune markers, may increase the potential of Pap smear in detecting extrauterine cancers (6).

The aim of this study was to analyse the clinicopathological features of eight extrauterine cancers diagnosed from abnormal Pap smear tests as the first manifestation of a malignancy. The role of the cervicovaginal smear in the diagnosis and management of these malignancies was also discussed.

MATRIALS AND METHODS

This was a retrospective analysis of patients with extrauterine tumors diagnosed initially with conventional Papanicolaou smear. This research was conducted in Ankara Research and Training Hospital. From a search of the pathology archives of our institution, the data were retrieved of eight patients from 2015 to December 2021 including cytosmears and corresponding histopathological sections. Approximately ten thousand pap smear reports during this period were scanned. Patients who had been diagnosed with cervical and vaginal cancers and any previous cancer at the time of screening were excluded. Ethical clearance for the study was obtained from the Institutional Ethics Committee. The study only included patients diagnosed with extrauterine cancers with a routine Pap screening test. Positive pap smears of patients with a known malignancy were excluded.

The clinical records, operative reports and data from patient files were obtained. The Pap smears from all eight cases were reviewed, and a record made of patient age, site of primary neoplasm, extent and distribution of the tumor and metastases. Primary involvement of the uterus/cervix/vagina was ruled out with clinical and histopathological examinations in all cases. Histopathological reports of colposcopy-directed biopsies, cervical biopsies, cone biopsies, fractional curettage, and hysterectomies were reviewed for the presence of typical and atypical glandular cells.

All the Pap smears were obtained with a routine procedure. There were at least two smears prepared for each case, which were immediately fixed in methanol and stained using the standard Pap staining technique. Each smear was studied according to the 2001 Bethesda system. Immunohistochemistry studies were performed on paraffin-embedded tissue sections. Details of cytopathological features and clinical features are listed in Table 1.

RESULTS

The mean age of the eight patients was 59 years (range, 42– 75 years). None of the cases had a history of carcinoma at the time of the Pap smear evaluation. Pelvic pain, vaginal bleeding or spotting was the presenting symptom in two cases. The clinical details of the patients with primary sites of extrauterine cancers are listed in Table 1.

Table 1. Demographic and clinicopathologic features of the patients

No	Age	Complaint	Diagnosis	Stage	Treatment
1	68	None	Transitionel cell ca		Transurethral resection (TUR)
2	42	Pelvic pain	Tubal cancer	1a	TAH+BSO+BPPLND+Omentectomy
3	56	None	Ovarian cancer	1c	TAH+BSO+BPPLND+Omentectomy
4	65	None	Ovarian cancer	3b	TAH+BSO+BPPLND+Omentectomy
5	72	Abnormal bleeding	Ovarian cancer	3c	TAH+BSO+BPPLND+Omentectomy
6	75	None	Ovarian cancer	3c	TAH+BSO+BPPLND+Omentectomy
7	47	None	Lymphoma		Simple hysterectomy
8	48	None	Clear cell ca ovarian	1a	TAH+BSO+BPPLND+Omentectomy

Of the eight patients, six were asymptomatic. In the two patients with symptoms (Patients 2 and 5), the time interval between the onset of symptoms and detection of a positive Pap smear was 2 and 3 months, respectively.

The histological types of the various extrauterine carcinomas in the eight patients were as follows: ovarian adenocarcinoma; transitional cell carcinoma of bladder, tubal cancer, clear cell cancer of over and large cell lymphoma. Three of these eight cases had widespread disease but none of the patients had metastasis to the vagina or cervix. Two patients with ovarian papillary serous carcinoma had malignant effusion and one had ovarian carcinoma with involvement of both fallopian tubes and omentum. Total abdominal hysterectomy was the most common surgical treatment followed by radical hysterectomy. Six of the eight patients received chemotherapy.

Cytomorphological examinations showed clusters of atypical cells with prominent nucleoli, nuclear groove, nuclear membrane irregularity and scanty cytoplasm admixed with normal endocervical and squamous cells on a clear background. Cellular features such as prominent nucleoli and nuclear longitudinal groove suggest bladder origin (Figure 1a,b,c).

Figure 1: Cervical examination smear revealed a clean background, showing mature, normal cervical elements and numerous highly atypical, hyperchromatic, epithelial cells with large nuclei featuring palisading arrangement. (A: Papanicolaou, x200; arrows show atypical cells with hyperchromatic nucleus) (B: Papanicolaou, x400) (C:Transitional cell carcinoma of bladder (Bladder-TUR))

Figure 1A

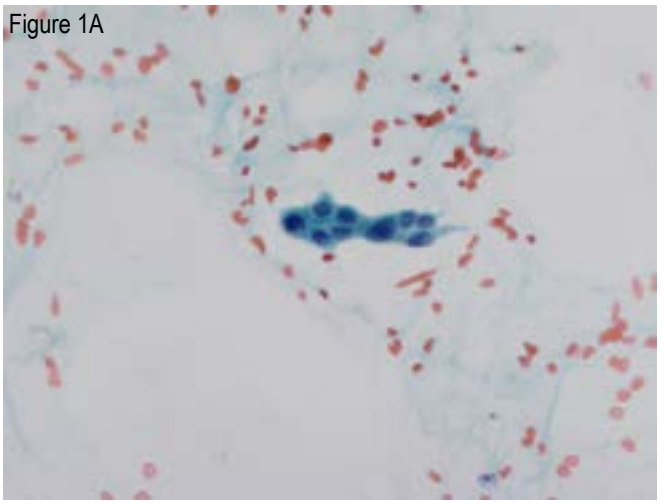


Figure 1B

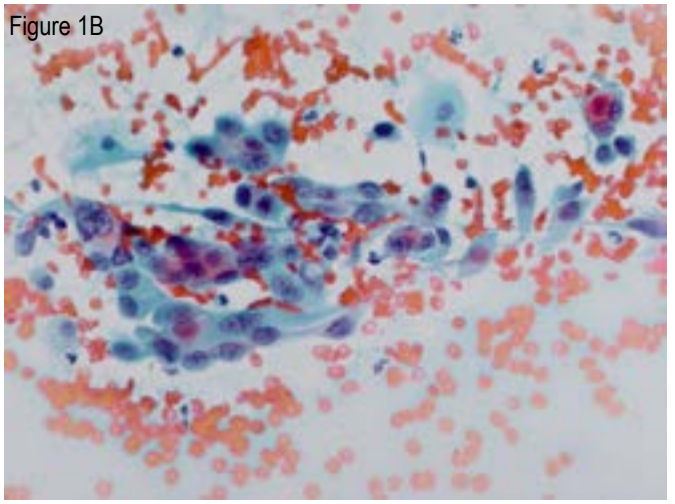
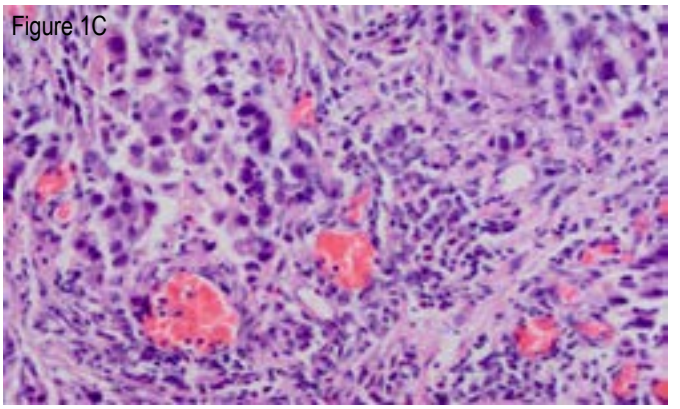


Figure 1C



The conventional Pap smear was atrophic backround in patient 8 with clear cell ovarian carcinoma. Some malignant cells with coarse chromatin, irregular nuclear membrane, vacuolar cytoplasm were noticed in the atrophic background (Figures 2a,b,c). The conventional Pap smear was atrophic backround in patient 8 with clear cell ovarian carcinoma. Some malignant cells with coarse chromatin, irregular nuclear membrane, vacuolar cytoplasm were noticed in the atrophic background (Figures 2a,b,c).

Fig. 2. Clear cell / Patient 8 A-B: Cervical smear examination demonstrating atypical cells of epithelial origin on a background of intermediary and parabasal cells together with neutrophils and leukocytes. (A: Papanicolaou, x500) C: Diffuse and strong CEA staining: Endometrial Biopsy

Figure 2A

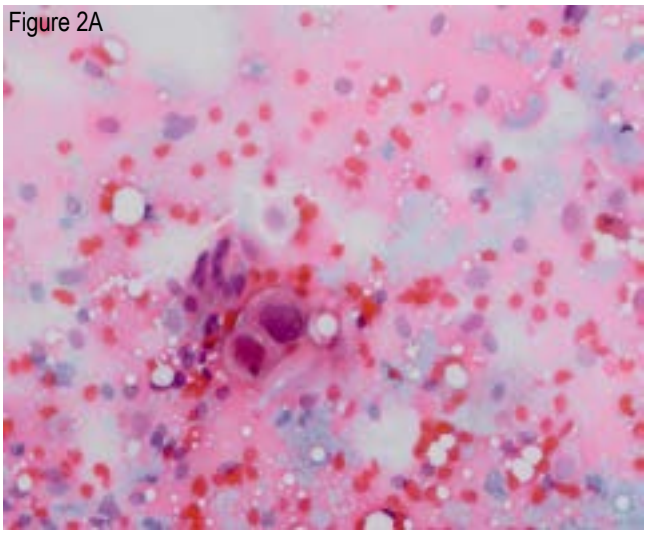
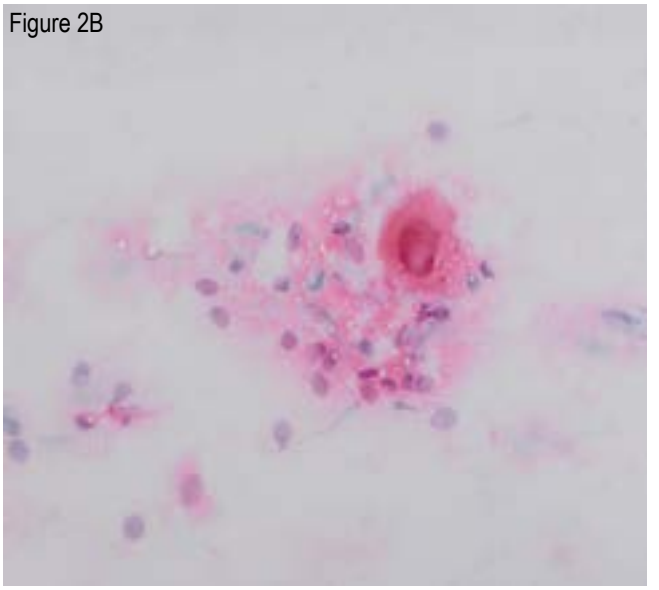
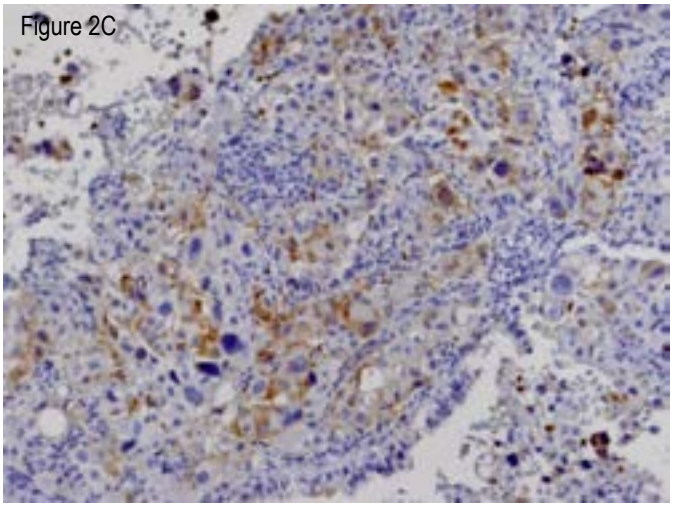


Figure 2B

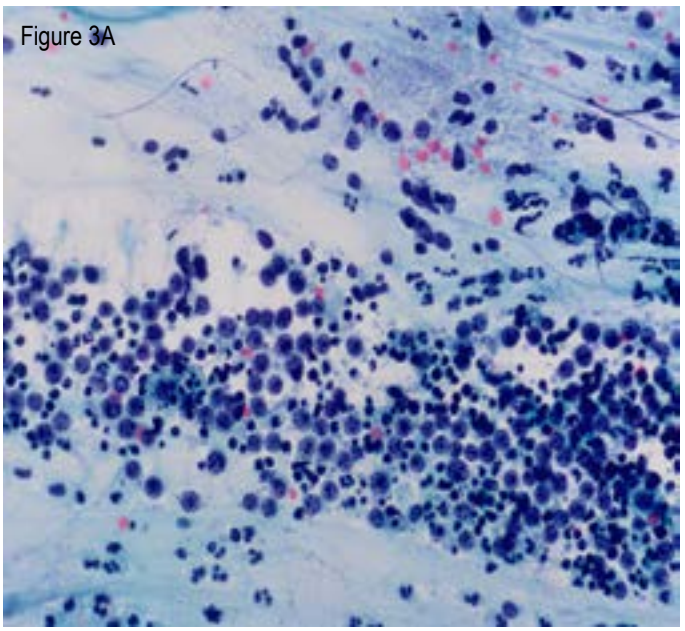


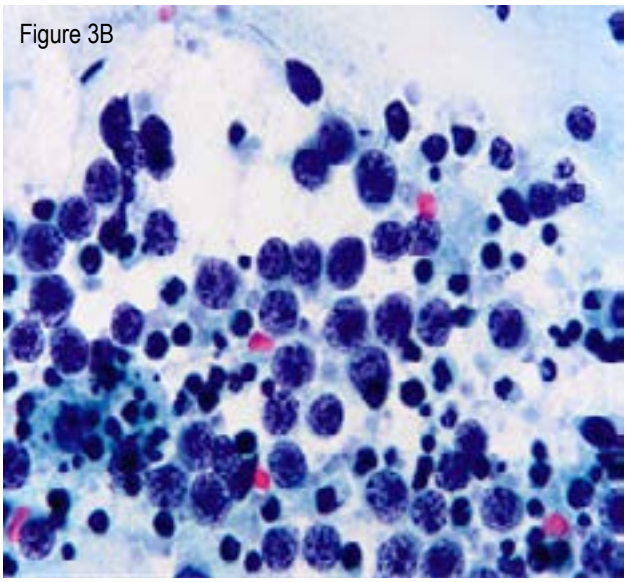


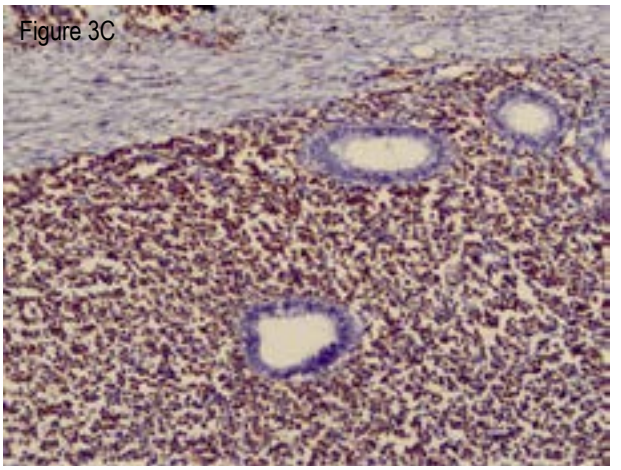
Epithelial cell abnormality, and atypical glandular cells, suggestive of endometrial or endocervical origin confirmed the diagnosis. Endometrial clear cell carcinoma diagnosis was made with endometrial biopsy. The Ki67 index was 80%. CEA was diffuse positive but vimentin, p53, MUC5ac, ER and progesterone were negative in the immunohistochemistry examination. But in this patient initial onset was ovarian origin.

Atypical appearing lymphoid cell groups admixed with normal squamous cells, endocervical cells and neutrophils were seen in a patient with lymphoma. The lymphoid cells were uniform, showing nuclear abnormalities including nuclear membrane irregularities and coarse uneven chromatin and several small nucleoli (Figure 3a,b,c).

Fig. 3. Lymphoma Patient 7 : Cervical examination smear showing atrophic background and groups of atypical cells of epithelial origin on a background of intermediary and parabasal cells together with neutrophils and leukocytes. (A-B: Papanicolaou, x500) C: Atypical lymphoid cells Show strong and diffuse immunreactivity for CD20 in curretage material.







After resection, microscopic examination demonstrated diffuse infiltration of the stroma and endometrial tissue by a monomorphic population of the malignant lymphoid cells Immunohistochemical studies showed that the neoplastic cells were only positive for B cell markers. A diagnosis of “Diffuse Large B cell non-Hodgkin’s Lymphoma” was made Most reports on extrauterine malignant tumors on routine Pap smears are single case reports (4,7,8,9). Most of the cases have a known history of extrauterine cancer and the appearance of malignant cells on a Pap smear is accepted as metastatic involvement (4,10). In one of the largest published reports, Gupta et al reviewed approximately 900,000 smears in a period of more than 20 years and detected only 33 (0.004%) cases with extrauterine cancer. The vast majority had a history of cancer at the time of the abnormal Pap smear (85%) (4). Although extremely rare, malignant cells in a cervical smear may be the first manifestation of extrauterine malignancy (9). To the best of our knowledge, our series of eight patients diagnosed from a Pap smear is one of the largest and demonstrates that Pap smears can also be effective in the early detection of such tumors. Half of the patients in this series were totally asymptomatic and the other half had non-specific symptoms of abnormal bleeding.

DISCUSSION

Malignant cells seen on Pap smears from extrauterine cancers can come from direct extension to the cervix or vagina, as a result of vascular metastasis or as exfoliated cells shed down the fallopian tubes (4,11). The presence of extrauterine cancer

cells in Pap smears also depends upon the site, presence of ascites and patency of fallopian tubes (12). Given the small dimensions of the cervix, the high content of fibrous tissue and lymphatics draining away makes the cervix unfavourable to metastasis but abnormal Pap smears may indicate an advanced disease in a patient with known extrauterine cancer (13). Of the eight patients in the current series, seven had no direct extension to the cervix of cervical metastasis, making passage though the fallopian tubes seemingly the most common mechanism. There were also no ascites detected in any of these patients.

The most common primary sites of extrauterine cancer are ovary, gastrointestinal tract, fallopian tube and breast. Extracervical malignancies on Pap smears are usually of a glandular nature and are rarely squamous carcinomas, sarcomas or lymphomas (14,15) The metastasis may be recognized by unique cytological features or because of the unusual presence of atypical cells different from the normal cervicovaginal cell pattern. The majority of metastatic tumors are characterized by a clean background or absence of tumor diathesis (1) The patient with transitional cell carcinoma in the current series had a clean background. Serous and clear cell carcinoma cells shed single cells, whereas endometrioid carcinoma cells shed cell groups and papillary structures (12). Patient no 2 in the current series had papillary structure and cell groups, and Patient no 3 had dispersed single tumor cells.

In the scenario of very limited atypical cells, molecular technologies may aid the diagnosis. Kinde et al. demonstrated that massively parallel sequencing of somatic mutations in DNA shed from ovarian cancers could be detected in standard liquid-based Pap test specimens (6). Arildsen et al. also detected a mutation in an archival sample of Pap smear obtained 20 months prior to the ovarian cancer diagnosis (16). Similarly, Wang et al. were able to identify the mutations in routinely collected Pap smears from the cervix in 33% of previously diagnosed ovarian cancer and 81% of previously diagnosed uterine cancer. Combining cervical sampling with a plasma test for circulating tumor DNA has been shown to further increase the ovarian cancer detection rate (17).

CONCLUSION

From the results of this study, it can be speculated that Pap smear, especially in cases of abnormal glandular cytology, may be associated with extrauterine cancer. Rigorous screening and precise morphological analyses with an extensive clinical approach are vital for diagnoses of extragenital malignancies. Large-scale investigations with more subjects and investigation of molecular methods for more extensive detection may enlarge the role of Pap smear in the detection of extrauterine cancers.

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Geriatrik Yaş Grubunda Over Kanseri Tanısıyla Takip Ettiğimiz Hastaların Kliniko-patolojik Özellikleri

Clinico-pathological Characteristics of Patients Diagnosed with Ovarian Cancer in the Geriatric Age Group

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ÖZ

Amaç: Bu çalışma geriatrik yaş grubunda over kanseri tanısıyla primer sitoredüktif cerrahi ile neoadjuvan kemoterapi sonrası interval cerrahi uygulanan hastaların kliniko- patolojik sonuçları ve postoperatif morbiditelerini karşılaştırmak amacıyla planlanmıştır.

Metod: 01.03.2019-01.03.2023 tarihleri arasında geriatrik yaş grubunda over kanseri olgularını içeren 103 hastanın kayıtları retrospektif olarak incelenmiş ve hastalar primer sitoredüktif cerrahisi ile neoadjuvan kemoterapi sonrası uygulanan interval cerrahi olarak iki grupta incelenmiştir. Hastalar komorbit hastalıkları, preoperatif CA-125 düzeyleri, hemoglobin düzeyleri, uygulanan tedavi seçenekleri, cerrahi sonrası histo-patolojik sonuçları, hastanede yatış süresi ve postoperatif komplikasyonlar açısından karşılaştırmalı olarak incelenmiştir.

Bulgular: 108 hastanın %47.6'sı (n:49) primer sitoredüksiyon alan grup, %52.4'ü (n:54) neoadjuvan kemoterapi sonrası interval cerrahi alan grup oluşturmaktaydı. Neoadjuvan alan grup istatiksel olarak anlamlı düzeyde daha fazla seröz histoloji (p=0.04), ileri evre (p=0.002), lenf nodu diseksiyonu operasyonu (p=0.002), ve CA-125 (p< 0.001) yüksekliği ile ilişkiliydi. Hastaların % 98.1'ine maksimal sitoredüksiyon ve %1.9'una suboptimal cerrahi uygulandı. Neoadjuvan kemoterapi sonrası interval cerrahi alan grup ile primer sitoredüksiyon alan grup arasında operasyon tipi, hastanede yatış süreleri, komorbidite ve yara yeri komplikasyonu açısından istatiksel olarak anlamlı fark izlenmedi.

Sonuç: Geriatrik yaş grubundaki over kanseri hastalarında maksimal sitoredüksiyon oranları yüksekti. Neoadjuvan kemoterapi sonrası interval cerrahi alan grup ile primer sitoredüktif cerrahi alan grub arasında maksimal sitoredüksiyon ve postoperatif komplikasyonlar açısından fark izlenmedi. Cerrahi sonuçları ve postoperatif morbiditeyi en aza indirmek için tersiyer merkezlerde jinekoloji onkoloji konusunda spesifikleşmiş merkezlerde hastaların tetkik ve tedavi edilmesi önem taşıyabilir.

Anahtar Sözcükler: Geriatri, over kanseri, primer sitoredüktif cerrahi, neoadjuvan kemoterapi, postoperatif komplikasyon

ABSTRACT

Objective: This study aimed to compare clinicopatolojic risk factors and postoperative morbidity of primary cytoreductive surgery and neoadjuvant chemotherapy followed by interval cytoreductive surgery.

Study Design: Between January 2019 and January 2023, 103 cases who had ovarian cancer with patients evaluated retrospectively in two groups as primary cytoreductive surgery and neoadjuvant chemotherapy followed by interval cytoreductive surgery. The cases in two groups were compared for comorbidities, CA-125 levels, hemoglobin levels, types of surgery histopathological results, length of hospital stay and postoperative complications.

Results: Of the 108 patients, 49 (47.6.5%) underwent primary cytoreductive surgery, and 54 (52.4%) had neoadjuvant chemotherapy followed by interval cytoreductive surgery. Compared with primary cytoreductive group, neoadjuvant group was associated with significantly more serous histology (p=0.04), advanced stage (p=0.002), lymph node dissection operation (p=0.002), and increased CA-125 (< 0.001). 98.1% of the patients underwent maximal cytoreduction and 1.9% suboptimal surgery. There was no statistically significant difference between the neoadjuvant group and the primary cytoreduction group in terms of operation type, length of hospital stay, comorbidity and wound complications.

Conclusion: The rates of maximal cytoreduction were high in ovarian cancer patients in the geriatric age group. There was no difference between neoadjuvant chemotherapy followed by interval surgery group and received primary cytoreductive surgery groups in terms of maximal cytoreduction and postoperative complications.In order to minimize surgical outcomes and postoperative morbidity, it may be important to examine and treat patients in centers specialized in gynecology oncology in tertiary centers.

Keywords: Geriatrics, ovarian cancer, primary cytoreductive surgery, neoadjuvant chemotherapy, postoperative complication

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GİRİŞ

65 yaş ve üzeri geriatrik yaş grubu olarak tanımlanır. Geriatri yaş popülasyonu sağlık hizmetlerinin artmasına paralel olarak tüm Dünya'da ve ülkemizde hızla artmaktadır (1,2). Günümüzde yaşlı nüfusun sayısının artmasına bağlı olarak over kanseri olgularına daha sık rastlanmaktadır. Over kanser Dünya'da jinekolojik kanserler arasında 3. sıklıkta görülür ve mortalite oranı jinekolojik kanserler arasında ikinci sıradadır (3). Over kanserlerin ortalama görülme yaşı 63'dür ve sıklıkla 55-64 yaş aralığında tanı alırlar. Over kanseri tanısı alan hastaların %47'sini 65 yaş üstü, %23 oranında da 75 yaş üzeri hastalar oluşturmaktadır (4).

Geriatri yaş grubunda görülen over kanser hastalarında uygulanan tedavi seçenekleri neoadjuvan kemoterapiyi takiben interval cerrahi veya primer sitoredüktif cerrahi takiben gerekirse uygulanan adjuvan kemoterapidir. Over kanserinde tedavi hastalığın yaygınlığına, hastanın komorbiditesine ve performansına göre belirlenir (5).

Geriatri yaş grubunda hastaların azalmış organ fonksiyonları ve sıklıkla eşlik eden kronik sistemik hastalıklarından ötürü seçilen tedaviden bağımsız olarak cerrahi ve kemoterapinin birçok zorlukları vardır (6,7). Bu yaş grubunda hastalar malignitenin geliştirdiği acil durum yaratan rahatsızlıklar ve yan etkilerden genç yaş grubuna göre daha fazla etkilenirler ve organ fonksiyon bozuklukları daha sık gözlenir. Geriatri yaş grubunda over kanseri tanısı konulan hastalar genellikle ileri evrede (evre III-IV) tanı alırlar ve 5 yıllık toplam sağ kalım oranları 70 yaş üzeri hastalarda %20'nin altındadır (8).

Ülkemizde ve dünyada geriatrik over kanseri olguları ile çok az sayıda çalışma bulunmaktadır ve bu yaş grubu çalışmalarda çoğunlukla ihmal edilmektedir. Artan geriarik nüfus nedeniyle over kanseri hastalarına uygulanan tedavi yaklaşımları bu yaş grubunda giderek önem kazanmaktadır. Bu çalışmanın amacı over kanseri tanısıyla jinekolojik onkoloji cerrahisi kliniğinde tetkik ve tedavi edilen geriatrik hastaların demografik verilerini, uygulanan tedavi seçeneklerini, patoloji sonuçlarını ve hastanede yatış sürelerini değerlendirmektir.

GEREÇLER VE YÖNTEM

Ankara Bilkent Şehir hastanesi ve Zekai Tahir Burak Eğitim ve Araştırma Hastanesi jinekolojik onkoloji kliniğine 01.03.2019-01.03.2023 tarihleri arasında geriatrik yaş grubunda over kanseri olgularını içeren retrospektif çalışmamızın etik kurul onayı alınmıştır (No:E2-23-4275). Over kanseri tanısıyla tetkik ve tedavi edilen toplam 285 hastanın kayıtları retrospektif olarak incelendi. Çalışmaya; epitelyal, germ ve seks kord hücreli hücreli over kanseri tanısı alan 65 yaş ve üzeri hastalar dahil edildi. 65 yaş altı over (epitelyal, germ ve seks kord hücreli) kanseri tanısı alanlar, borderline over tümör tanısı alan, daha önce başka bir malignite tanısı ile tedavi edilen, çift primer kanser tanısı alan ve düzenli takiplere gelmeyen hastalar çalışma dışı bırakıldı. Hastalardan girişimsel radyoloji bölümünde ultrasound eşliğininde tri-cut yöntemi ile biyopsi veya ince iğne aspirasyon biyopsisi yöntemi ile batın sitoloji alınarak over kanser tanısı alan hastalar neoadjuvan kemoterapi verildi. Bu hastalara cerrahi operasyon öncesi 3-4 kür karboplatin ve paklitaxel kemoterapi tedavisi verildikten sonra interval cerrahi uygulandı. Neoadjuvan kemoterapi aldıktan sonra progresif hastalık nedeniyle cerrahi tedavi için uygun olmayan veya cerrahi tedaviyi kabul etmeyen 16 hasta çalışma dışı bırakıldı. Kalan 103 hasta 2 grupa sınıflandırıldı. Neadjuvan kemoterapi sonrası interval cerrahi grubu (n:49) ve pirimer sitoredüktif cerrahi (n:54) grup olarak kategorize edildi. Yaş, demografik özellikler, tümörün histopatolojik incelemesi, evre, preoperatif hemoglobin düzeyi, Ca-125 düzeyi, neoadjuvan tedavisi alıp almadığı, adjuvan tedavi alıp almadığı, hastanede yatış süresi, postoperatif yara yeri enfeksiyonu gelişip gelişmediği, sekonder sütür atılıp atılmadığı ve komorbit hastalıkları (diyabetes mellitus, hipertansiyon, koroner arter hastalığı, kronik akciğer hastalıkları, kronik böbrek hastalıkları) kaydedildi. Hastalar 2018 Uluslararası Jinekoloji ve Obstetri Derneği (FIGO) over kanseri evreleme sistemine göre evrelendirildi (9). Cerrahi geçiren tüm hastalara operasyondan 30 dak önce profilaktik antibiyoterapi uygulandı. Postoperatif 30 gün süresince insizyon hattında akıntı, kızarıklık gibi semptomlarla başvuran, yara yeri açılan, kültürde yara yerinde enfeksiyonu olan hastalar cerrahi yara yeri komplikasyonu olarak tanımlandı. Operasyonunda en fazla total abdominal histerektomi, bilateral salpingooferektomi, total omentektomi ve bilateral pelvik paraaortik lenf nodu diseksiyonu yapılanlar minör cerrahi operasyon grubu olarak kabul edildi. Bu işlemlere ek olarak intraabdominal yapılan cerrahi girişimlerin (splenektomi, pankreatektomi, kardiofrenik lenf nodu diseksiyonu, karaciğer metastetektomi, ince bağırsak, kolon rezeksiyonu ve anastomozları) bulunması majör cerrahi operasyon grubu olarak tanımlandı. Operasyon bitiminde gözle görülen rezidü tümör yok ise maksimal sitoredüksiyon (Ro), R 1< 1 cm ise optimal sitoredüksiyon ve R2 ≥1 cm ise suboptimal sitoredüksiyon olarak tanımlandı. Hastaların klinik ve patolojik verileri hastanenin elektonik veri tabanından ve hasta dosyalarında elde edildi.

İstatistik analiz

İstatiksel analiz için SPSS 25.0 versiyon yazılımı kullanıldı. Verilerin normal dağılıma uygunluğu histogram, olasılık grafikleri ve Kolmogorov-Smirnov testi ile değerlendirmiştir. Sayısal değişkenler sayı ve yüzde olarak belirtildi. Sayısal değişkenler ortalama ± standart sapma ve ortanca (minimum- maksimum) olarak sunuldu. Sürekli değişkenlerin analizinde Mann-Whitney U testi kullanıldı. Kategorik değişkenleri analiz etmek için chi square testi uygulandı. Anlamlılık düzeyi P<0.05 olarak kabul edildi.

BULGULAR

Çalışmaya kayıtlarına ulaştığımız 65 yaş ve üzeri over kanseri tanısı olan 103 hasta dahil edilmiştir. Tüm kohortun kliniko-patolojik özellikleri Tablo 1 de sunulmuştur. Hastaların medyan yaş ortalamasın 71.2 (65-82) olarak bulundu. Hastaların bakıldığında 92 (%89.34)'si yüksek dereceli seröz karsinom, 6 (%5.9)'sı seks kord hücreli karsinom, 2 (%1.9)'si düşük gradeli seröz karsinom, 2 (%1.9)'si mikst hücreli karsinom ve 1 (%1)'i müsinöz karsinom histopatolojik tanısına sahipti. Tüm kohortun % 90 (%87.4)'ı ileri evre (evre 3-4)'idi. Hastaların %51.5 (n:53)'i evre 3C olarak saptandı.

Table 1: Çalışmaya dahil olan hastaların kliniko-patolojik özellikleri

Karakteristik	Değerler
Yaş (ortalama, yıl)¥	71.23 ± 5.21
Hemoglobin (gr/dl)¥	12 ± 1.54
Ca-125 (U/ml)¥	808.8 ± 13282.26
Hastanede yatış süresi (gün)¥	9.34 ±4.98
Histopatoloji n (%)	
Yüksek dereceli seröz karsinom*	92 (% 89.3)
Düşük dereceli seröz karsinom*	2 (%1.9)
Müsinöz karsinom*	1 (%1)
Mikst hücreli karsinom*	2 (%1.9)
Seks-kord hücreli karsinom*	6 (% 5.9)
FIGO evre 2018	
1a*	4 (%3.9)
1b*	2 (%1.9)
1c2*	1 (%1)
1c3*	1 (%1)
2a*	2 (%1.9)
2b*	3 (%2.9)
3a1.2*	3 (%2.9)
3b*	2 (%2.9)
3c*	53 (%51.5)
4a*	1 (%1)
4b*	31 (%30.1)
Komorbit hastalıkları*	
Diyabetes Mellitus*	37 (%35.9)
Hipertansiyon*	67 (%65)
Koroner Kalp Hastalığı*	10 (%9.7)
Akciğer Hastalığı*	6 (%5.8)
Böbrek Hastalığı*	4 (%5.8)
Lenf nodu yapılmış*	78 (%75.7)
Adjuvan tedavi verilmiş*	98 (%95.1)
Yara yeri enfeksiyonu*	7 (%6.8)
Sekonder sütürasyon*	8 (%7.8)

¥ Değerler ortalama±standart sapma olarak verilmiştir.

*Değerler n (%) olarak verilmiştir.

Neoadjuvan alan grup istatiksel olarak anlamlı düzeyde daha fazla seröz histoloji, ileri evre, lenf nodu diseksiyonu operasyonu ve ca-125 yüksekliği ile ilişkiliydi (Tablo 2).

Table 2: Neoadjuvan kemoterapiyi takiben interval cerrahi uygulanan grup ile primer sitoredüktif cerrahi geçiren grubun klinik-patolojik özelliklerinin karşılaştırması

Klniko-patolojik özellikler			
	Neoadjuvan kemoterapi takiben interval cerrahi grup (n=54)	**Primer sitoredüktif cerrahi grup (n=49)**	**P değeri**
Histopatolojik tip			
Seröz	53	1	**0.04***
Nonseröz	1	6	
Evre			
Erken Evre (1-2)	1	12	**0.002***
Geç Evre(3-4)	53	37	
Lenf nodu yapılmış			
Evet	34	44	**0.002***
Hayır	20	5	
Lenf nodu metastazı			
Evet	17	28	**0.008***
Hayır	37	21	
Operasyon tipi			
Minör operasyon	30	32	0.210
Major operasyon	24	17	
Yara yeri enfeksiyonu			
Evet	4	3	0.55
Hayır	50	46	
Hastanede yatış (ortalama, gün)	9.8±5.4	8.7±4.4	0.44
Ca-125	1277.67±1721.98	292.1±515.9	**< 0.001***

*p<0.05 istatiksel anlamlıdır.

Primer sitoredüktif cerrahi grubunda istatiksel olarak anlamlı lenf nodu metastazı bulundu. Hastaların 77 (%74.7)'sinde en az bir medikal komorbidite saptandı. Tüm kohortun %47.6'sı (n:49) primer sitoredüksiyon cerrahi alan grup, %52.4'ü (n:54) neoadjuvan kemoterapi takiben interval cerrahi alan grup oluşturmaktaydı (Tablo 2). Hastaların % 98.1'ine (n:101) maksimal sitoredüksiyon ve %1.9'una (n:2) suboptimal cerrahi uygulandı. Hastaların % 60.2'sine (n:62) minör cerrahi ve %39.8'ine (n:41) majör cerrahi operasyon uygulandı. Tüm kohortta cerrahi yara yeri komplikasyonu 7 (%6.8) olarak saptandı. Tüm kohortun hastanede yatış süresi 9.34 4.98 gün olarak bulundu. Neoadjuvan grup ile primer sitoredüksiyon grubu arasında operasyon tipi, hastanede yatış süreleri, komorbidite ve yara yeri komplikasyonu açısından istatiksel olarak anlamlı fark izlenmedi.

TARTIŞMA

Türkiye istatistik kurumunu verilerine göre yaşlı nüfus oranının 2023 yılında %10.2, 2050 yılında ise %20,8'e yükseleceği belirtilmiştir (10). Nüfus yaşlanması arttıkça ileri yaşlarda over kanseri saptanma oranı artmaktadır. İleri yaşın over kanseri hastalarında morbidite ve mortalitede kötü bağımsız prognostik faktör olduğu yapılan çalışmalarda gösterilmiştir(11,12).

Deng ve arkadaşları over kanserine sahip 65 yaş ve üzeri hastalarda yüksek histolojik dereceli tümör, kötü performans durum ve suboptimal cerrahi oranının genç yaş hastalara göre daha sık olduğunu bildirmişlerdir (13). Benzer başka bir çalışmada, Gottwald ve arkadaşları 70 yaş üstü geriatrik over kanseri hastaların tanı anında ileri evre olduğunu ve tedavilerinde daha az radikal cerrahi uygulandığını bildirmişlerdir (14). Diğer taraftan Ben-Ami ve arkadaşları 70 yaş üstü over kanseri hastalarında ileri evre saptanma oranı ve operasyon sonunda maksimal sitoredüksiyon sağlama oranının genç yaşa grubuna göre fark olmadığını bildirmişlerdir. Yaşın tek başına postoperatif komplikasyonlar ve cerrahi sonuçlar için zayıf bir prediktör olduğunu ve cerrahiye engel olmadığı vurgulamışlardır (12) (15).

Over kanserlerinin en sık görülen histolojik tipi epitelyal hücrelerden kaynaklanır. Epitelyal over kanserlerinin en sık görülen histopatolojik tipi ise yüksek dereceli seröz karsinom olup oranı %50'dır. Diğer tipler, düşük dereceli seröz karsinom (%10), endometroid karsinom (%10), müsinöz karsinom (%10) ve clear cell karsinomlar (%5)'dır. Geri kalan kısmını seks kord stromal tümörler (%5-8) ve germ hücreli tümörler (%3-5) oluşturur (16). Çalışmamızda en sık görülen over kanseri histopatolojik tipi yüksek dereceli seröz karsinomdur 92 (%89.3).

Cerrahi alan enfeksiyonları postoperatif morbidite ve mortaliteyi arttırmasının yanısıra hastanede yatış süresini etkilemesi, tekrar hastaneye başvurma sıklığını arttırmasından ötürü ülkenin sağlık harcamalarını arttırarak ülke ekonomisine de negatif etkisi bulunmaktadır. Falandry ve arkadaşlarının yaptığı 70 yaş ve üzeri neoadjuvan kemoterapi alıp interval cerrrahi yapılan over kanseri hastalarında yara yeri enfeksiyonu ve diğer perioperatif komplikasyon oranların primer sitoredüktif cerrahi gruba istatiksel olarak anlamlı düzeyde düşük olduğunu bildirmişlerdir(12). Çalışmamızda neoadjuvan yapılan grup ile primer cerrahi yapılan grup arasında yara yeri enfeksiyonu açısından istatiksel olarak anlamlı ilişki saptanmamıştır.

Coleridge ve arkadaşlarının yaptığı meta-analizde neoadjuvan kemoterapi alan grupta primer sitoredüktif cerrahi yapılan grupa göre daha az major cerrahinin uygulandığı ve operasyon süresinin daha kısa olduğu bildirilmiştir (17). Machida ve arkadaşlarının yaptığı meta-analizde de benzer olarak neoadjuvan kemoterapi alan grupta primer sitoredüktif cerrahi yapılan grupta daha kısa operasyon süresı ve daha az majör operasyon (daha az intestinal organ rezeksiyonu) saptamışlardır(18). Bununla birlikte, Filippova ve arkadaşlarının yaptığı çalışmada geriatrik yaş grubu hastalar arasında neadjuvan sonrası interval cerrahi yapılan grup ile primer sitoredüktif cerrahi geçiren grup arasında maksimal sitoredüksiyon oranları arasında istatiksel fark izlenmemiştir (5). Çalışmamızda geriatrik yaş grubunun %87.4'ünün ileri evre (evre3-4)'de olduğu saptandı ve bunların % 98' ine maksimal sitoredüksiyon operasyonunun sağlandığı bulunmuştur. İleri yaş (65) hastalarda neadjuvan alan grup ile primer sitoredüktif cerrahi yapılan grup arasında maksimal sitoredüksiyon açısından anlamlı fark saptanmamıştır. Bunun sebebi olarak operasyonun jinekolog onkoloji biriminin bulunduğu tersiyer merkezde yapılmış olması öne sürülebilir.

CA-125, MUC16 geni tarafından kodlanan tümör belirteçidir. Bu belirteçler over kanserlerinde tümörün yaygınlığını, malignite tedavisine cevabı ve nüksü değerlendirmede kullanılır. CA-125 sensivite ve spesifitesi malignite için düşüktür. Benign jinekolojik rahatsızlıklar (adenomyozis,endometriozis, pelvik inflamatuar hastalıklar), gebelik gibi durumlarda serum düzeyi yükselebilir (19). Bu çalışmada neoadjuvan kemoterapi alan grupta CA-125 değerleri primer sitoredüktif cerrahi grubuna göre istatiksel olarak anlamlı yüksek bulunmuştur. Hasta sayısının kısıtlı olması, kısa izlem süresi ve tek merkez olması çalışmanın limitasyonlarıdır. Avantajları ise ülkenin çeşitli bölgelerinden gelen hastaların tedavi edildiği referans hastane olmasıdır.

SONUÇ

Nüfus yaşlanmasına bağlı olarak ülkemizde ileri yaş nüfüs sayısı artmaktadır ve ileri yaş grubunda saptanan over kanseri hasta sayısı artmaktadır. Çalışmamızda maksimal sitoredüksiyon ve postoperatf cerrahi komplikasyon oranı açısından neoadjuvan grubu ile primer sitoredüktif cerrahi grubu arasında fark saptanmamıştır. İleri yaş bu hastalar için cerrahi tedaviye engel olmamalıdır. Bu yaş grubunda over kanseri nedeniyle yapılacak operasyonunu maksimal sitoredüktif cerrahinin yapılabileceği jinekolog onkologların ameliyat eşlik edeceği merkezlerde yapılması gerektiğini öneriyoruz.

Çıkar Çatışması

Yazar(lar) çıkar çatışması olmadığını bildirmişlerdir.

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Antenatal Bakım Almayan Suriyeli Sığınmacı Gebelerin Maternal ve Neonatal Sonuçlarının Değerlendirilmesi

Evaluation of Maternal and Neonatal Outcomes of Pregnant Syrian Refugees Not Receiving Antenatal Care

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ÖZ

Amaç: Antenatal bakıma ulaşamayan sığınmacı gebelerin maternal ve neonatal sonuçlarının değerlendirilmesi amaçlanmıştır.

Metod: Bu çalışmada bir eğitim ve araştıma hastanesi doğum salonuna Ocak 2013-Ocak 2015 tarihleri arasında yatırılan ve gebeliği boyunca takip almayan 202 Suriyeli sığınmacı gebe dahil edildi. Demografik, maternal ve neonatal sonuçları değerlendirildi.

Bulgular: Katılımcıların ortalama yaşı 23,9± 4,8, medyan gravida sayısı 3 ve medyan parite sayısı 1 idi. Gebelerin laboratuvar değerlerinin ortalaması sırasıyla hemoglobin 11,3 g/dl, ferritin 15,1 ng/ml, vitamin B12 179,5 pg/ml, demir 57,1 mcg/dl, folik asit 10 ng/ml, 25 hidroksi D (25 OH D) vitamin 6,6 ng/ml'dir. Gebelik komplikasyonlarına bakıldığında ; %19,2'sinde oligohidramnios, %3'ünde gebelik haftasına göre düşük doğum ağırlığı , %2'sinde anhidramnios, %1,5'inde intrauterin büyüme kısıtlılığı görülmüştür. Yenidoğanların ortalama doğum haftası 38, doğum ağırlığı ortalaması 3096 gr ve boy ortalaması 48,9 cm idi. Yenidoğanların üçünde polisitemi tespit edildi.Yenidoğanlarda tespit edilen anomaliler; nöral tüp defekti (n=1), hipoplastik sol kalp sendromu(n=1), duodenal atrezi(n=1), hidrosel(n=1), ambigus genitale(n=1), anensefali(n=1), fasial paralizi(n=1) ve özofagus atrezi(n=1) idi. Hastaların gebelik sayısı arttıkça hemoglobin, ferritin ve folik asit değerlerinin referans değerlerine göre anlamlı olarak azaldığı (sırasıyla p=0,036,p=0,012,p=0,044), demir değeri düşük olanların 1. ve 5. dakika Apgar skorunun anlamlı olarak daha düşük olduğu saptanmıştır (sırasıyla p<0,001, p=0,002). 25 OH D vitamin değeri ile ultrasonla ölçülen femur uzunluğu ve doğum boyu arasında anlamlı pozitif korelasyon olduğu tespit edilmiştir (sırasıyla p=0,020, p=0,050).

Sonuç: Sığınmacı gebelerde antenatal dönemde yeterli bakım alınmamasına bağlı olarak gebelik komplikasyonları ve olumsuz neonatal sonuçlar sıklıkla görülmektedir. Yetersiz antenal bakım hizmetinin maternal ve fetal etkileri üzerine hastalar bilgilendirilmeli, sağlık hizmetine kolayca ulaşmaları sağlanmalıdır.

Anahtar Kelimeler: Mülteci, antenatal bakım, perinatal sonuç, yenidoğan sonuç

ABSTRACT

Objective: We aimed to evaluate the maternal and neonatal outcomes of refugee pregnant women who could not reach antenatal care.

Study Design: In this study, 202 refugee pregnant women who were hospitalized in the delivery room of a training and research hospital between January 2013 and January 2015 and were not followed up during their pregnancy were included. Demographic, maternal, and neonatal outcomes of Syrian refugee pregnant women were evaluated.

Results: The mean age of the participants was 23.9±4.8 years, the median number of gravida was 3, and the median parity number was 1. The mean laboratory values of pregnant women were as follows; hemoglobin 11.3 g/dl, ferritin 15.1 ng/ml, vitamin B12 179.5 pg/ml, iron 57.1 mcg/dl, folic acid 10 ng/ml, and 25 hydroxy D vitamin (25 OH D) 6.6 ng/ml. Oligohydramnios was detected in 19.3% of the patients, low birth weight for gestational age in 3%, anhydramnios in 2%, and intrauterine growth retardation in 1.5%. The mean birth week of the newborns was 38, the mean birth weight was 3096 g, and the mean height was 48.9 cm. Polycythemia was observed in three of the newborns. Anomalies detected in newborns; neural tube defect (n=1), hypoplastic left heart syndrome (n=1), duodenal atresia (n=1), hydrocele (n=1), ambiguous genitalia (n=1), anencephaly (n=1), facial paralysis (n=1) and esophageal atresia (n=1). As the number of pregnancies of the patients increased, hemoglobin, ferritin, and folic acid values decreased significantly compared to the reference values (p=0.036, p=0.012, p=0.044, respectively), and the 1st and 5th minute Apgar scores of those with low iron values were found to be significantly lower(p=0.000, p=0.002, respectively). In addition, there was a significant positive correlation between the 25 OH vitamin D value and the femur length measured by ultrasound and birth length (p=0.020, p=0.050, respectively).

Conclusion: Pregnancy complications and adverse neonatal outcomes are frequently seen in refugee pregnant women due to insufficient care in the antenatal period. Patients should be informed about the maternal and fetal effects of inadequate antenatal care, and they should be provided with easy access to health services.

Keywords: Refugee, antenatal care, perinatal outcome, neonatal outcome

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GİRİŞ

Türkiye'de sığınmacı olarak barınan Suriyelilerin sağlık durumları ve sağlık gereksinimlerinin uygun biçimde karşılanması önemli bir halk sağlığı sorunudur. Mülteci olarak yaşamak, barınma, iş, yiyecek ve sağlık hizmeti eksikliği ve dil engelleriyle ilgili olmak üzere bir çok problemle ilişkilidir. Bu sorunlar nedeniyle mülteciler üreme sağlığı sorunları açısından dezavantajlı grupta yer almaktadır (1). Mülteci kamplarındaki kadın sağlığı ile ilgili hızlı değerlendirmeler kadınların %23 ünün üreme sağlığı hizmetleri hakkında habersiz olduklarını göstermektedir, %28 plansız gebelik yaşamakta olduğunu ve %17 sinin gebelik için antenatal bakıma ulaşamadığını göstermektedir (2).

Dünya Sağlık Örgütü (DSÖ)'nün yeni modeli antenatal bakıma gelen gebeleri sadece rutin antenatal bakım gereken gebeler ve bazı özel sağlık durumları ve risk faktörleri nedeni ile özel bakım gerektiren gebeler olarak iki gruba ayırmaktır. İlk gruba giren gebelere standart dört kez antenatal muayene önerilmekte, bu muayenelerde sadece gebe muayenesi ve amaca yönelik testler uygulanmaktadır. Bu antenatal bakım süreci ; birinci izlemin gebeliğin ilk 14 haftası içerisinde, ikinci izlemin 18-24. haftalar arasında, üçüncü izlemin 30-32. haftalar arasında ve dördüncü izlemin 36-38.haftalar arasında yapılmasını kapsar. Bu ziyaretlerle, gebelik komplikasyonları ve fetal anomaliler erken dönemde tanımlanır ve gerekirse müdahale edilerek anne ve bebek ölümleri engellenebilir (3, 4).

Tüm dünyada her yıl yaklaşık 600,000'den fazla kadın gebelik ve doğum komplikasyonları nedeniyle yaşamını yitirmektedir. Gelişmiş ülkelerde gebelik süresince en az bir kez izlem alan gebe oranı %98.0 iken, az gelişmiş ülkelerde bu oran %65'e kadar düşmektedir. Bu oran mültecilerde daha düşüktür. Türkiye'de gerçekleştirilen bir çalışmada mültecilerin %99'unun düzenli antenatal bakım almadığı tespit edilmiştir (5).

Yeterli seviyede doğum öncesi bakım alamayan göçmen kadınların maternal ve fetal olumsuz sonuçlar açısından riskli olduğu tespit edilmiştir. Erken doğum, postpartum kanama, perineal travma, pospartum depresyon ve sezaryen ile doğum oranlarının artmasının yanısıra fetal mortalite ve düşük doğum ağırlığı bu kadınlarda oldukça fazla görülmektedir (6).

Bu çalışmanın amacı Suriyeli sığınmacıların antenatal bakım almamalarının maternal ve neonatal sonuçlara etkisi olup olmadığını belirlemektedir. Bu nedenle doğum salonuna yatırılan antenatal takip almayan Suriyeli gebelerde, yatış anındaki labaratuar değerlerine göre maternal ve neonatal sonuçlarını belirlemeyi planladık.

GEREÇLER VE YÖNTEM

Bu retrospektif çalışmanın çalışma grubunu, bir eğitim araştırma hastanesi doğum salonuna Ocak 2013- Ocak 2015 tarihleri arasında yatırılan ve gebeliği boyunca antenatal bakım almamış 202 Suriyeli gebe oluşturmuştur. Çalışma Keçiören Eğitim Araştırma Hastanesi Etik Komitesi tarafından onaylanmıştır (B.10.4.İSM.4.06.68.49/). Dışlama kriterleri; Türkiye'de veya kendi ülkesinde antenatal takip alması veya gebeliği sırasında herhangi bir nedenle hastanede yatırılarak takip edilmesi ve kronik bir hastalığı bulunmasıdır.

Çalışmanın değişkenleri; Sağlık Bakanlığı tercüman hattı veya hastane tercümanı vasıtasıyla kayıt altına alınan yaş, gestasyonel hafta, gravide, parite, abortus, yaşayan bebek sayısı, daha önceki doğum şekilleri, dilatasyon/küretaj sayıları, reprodüktif öykü, membran rüptürü durumu, Rh uygunsuzluğu varlığı, gebelikteki hipertansif hastalık varlığı, gestasyonel diyabet durumu, kronik hastalık varlığı, doğum özelliklerine ve yenidoğan özelliklerine ilişkin değişkenlerdir. Reprodüktif öyküde önceki gebelikte intrauterin ölü fetus, postpartum ölü fetus durumu sorulmuştur. Bu değişkenleri takiben gebelere fizik, obstetrik ve sonografik muayene yapılmıştır. Sonografik muayenede prezentasyon, amniyon sıvı miktarı ve Biperietal Diameter (BPD), Abdominal Circumference (AC), Femur Length (FL) ölçümleri milimetre cinsinden ve ultrasonda karşılık geldiği gebelik haftası olarak kaydedilmiştir. Doğum salonuna kabulün ardından gebelerden tam kan sayımı, karaciğer ve böbrek fonksiyon testleri, ferritin, demir, demir bağlama kapasitesi, vitamin B12, folik asit, 25 hidroksi D vitamini (25 OH D) vitamin tetkikleri analiz edilmiştir. Referans aralığı için alt düzeyler hemoglobin (Hb) için 11g/dl, ferritin için 10 ng/ml, vitamin B12 için 200 pg/ml, demir için 28 mcg/dl, folik asit için 3 ng/ml, 25 OH D vitamin için 10 ng/ml nin altındaki değerler olarak alınmıştır(7). Doğum özelliklerine ilişkin değişkenler; doğum şekilleri, doğumda amniyon sıvısındaki mekonyum durumu, vajinal doğum yapanların epizyotomi durumları ve sezaryen doğum endikasyonları idi. Yenidoğan özelliklerine ilişkin değişkenler; cinsiyet, doğum ağırlığı ve boyu, 1. ve 5. dk Apgar skorları, morbidite durumları, konjenital anomali durumlarıdır.

İstatistiksel Analiz

Veriler SPSS 21.0 istatistik paket programı aracılığıyla değerlendirilmiştir. Tanımlayıcı istatistikler, ortalama ve standart sapma, ortanca (minimum-maksimum), sayı ve yüzde dağılımı olarak sunulmuştur. Değişkenler arasındaki ilişkiler Bağımsız T Testi ve Pearson korelasyon testi ile analiz edilmiştir. İstatistiksel anlamlılık değeri $p<0.05$ olarak kabul edilmiştir.

BULGULAR

Çalışmaya dahil edilen 202 gebenin sosyo-demografik özellikleri ve doğum sonuçları Tablo 1' de gösterildi. Katılımcıların sosyodemografik özelliklerinin ortalama değerleri; yaş 23,9, medyan gravida 3 ve medyan parite 1 idi. Obstetrik komplikasyonlarına bakıldığında ; oligohidramnios (%19,2), gebelik haftasına göre düşük doğum ağırlığı(%3) ,anhidramnios (%2), intrauterin büyüme kısıtlılığı (%1,5), makrozomik fetus (%1,5) olarak bulundu., Yenidoğanların %55,9'u erkek, doğum ağırlığı ortalaması 3096 gr,boy ortalaması 48,9 cm idi. Doğum şekilleri ve sezaryen endikasyonları da Tablo 1'de gösterilmiştir.

Yenidoğan sonuçları ise polistemi (n=3), nöral tüp defekti (n=1), hipoplastik sol kalp (n=1), duodenal atrezi (n=1), hidrosel (n=1), ambigius genitalya (n=1), anensefali (n=1), ve özefagus atrezi (n=1) şeklinde idi. Hastalara ait ortalama hemoglobin, ferritin, vitamin B12, demir, 25-OH D vitamini, folik asit değerlerine bakıldığında ise; hemoglobin 11,3 g/dl, ferritin 15,1 ng/ml, vitamin B12 179,5 pg/ml, demir 57,1 mcg/dl, folik asit 10 ng/ml, 25-OH D vitamin 6,6 ng/ml idi. Bu labaratuar parametreleri hastaların geçirdiği gebelik sayısına göre de karşılaştırıldı. kıyaslandığında; multiparların labaratuar parametrelerine karşılık ilk gebeliği olan hastaların ortalama hemoglobin değeri (11,2'ye karşılık 11,7, $p=0.036$), ferritin (13,1'e karşılık 18,9,$p=0.012$), folik asit (9,5'a karşılık 11,1, $p=0.044$) olarak bulundu.

Tablo 1. Olguların demografik özellikleri ve obstetrik sonuçları

		Tüm katılımcılar (n=202)
Yaş (yıl)		23,9±4,8
Gravida		3 (1-9)
Parite		1 (0-8)
Dilatasyon / küretaj		0 (0-1)
Abortus		0 (0-4)
Yaşayan		1 (0-8)
Obstetrik komplikasyon olmayan		145 (%71,8)
İntrauterin büyüme kısıtlılığı		3 (%1,5)
Gebelik haftasına göre düşük doğum ağırlığı		6 (%3)
Oligohidramnios		39 (%19,2)
Anhidramnios		4 (%2)
Polihidramnios		1 (%0,5)
Makrozomi		3 (%1,5)
Ablasyo plasenta		1 (%0,5)
Vajinal doğum	Spontan	135 (%67,6)
	Hariçte doğum	1 (%0,5)
Sezaryen endikasyonları	Geçirilmiş sezaryen öyküsü	24 (%12)
	Akut fetal distres	19 (9,4)
	Baş-pelvis uyumsuzluğu	7 (%3,5)
	İlerlemeyen eylem	5 (%2,5)
	Transvers	5 (%2,5)
	Makat prezentasyon	4 (%2)
	Makrozomi	1 (%0,5)
	Yüz geliş	1 (%0,5)

Değerler ortalama +/- standart sapma, ortanca (minimum maksimum), sayı (yüzde) olarak verildi.

Demir değerleri normal olanlar ile referans değerin altında olanların yaş, gravida, parite, doğum haftası, 1 ve 5. dakika Apgar skorları, doğum ağırlığı, boy karşılaştırılması yapıldı ve Tablo 2'de gösterildi. Yaş, gravida, parite, gebelik haftası, doğum ağırlığı, doğum boyu arasında anlamlı fark izlenmezken; 1. ve 5.dakika Apgar skorları demir değeri referans değerin (28 mcg/dl) altında olanlarda anlamlı olarak düşük bulunmuştur (sırasıyla 8,5'e karşılık 9,p=0.000, 9,5'e karşılık 9,7, p=0.002).

Tablo 2. Demir değerleri normal olanlar ve düşük olanlar arasında ile yaş, gravide, parite, doğum haftası, 1.dakika Apgar skoru, 5.dakika Apgar skoru, doğum ağırlığı, doğum boy değişkenlerinin karşılaştırılması

	Demir düşük (n=31)	Demir normal (n =171)	p değeri
Yaş	25 ± 5,8	23,7 ±6,1	.255
Gravide	2,6 ± 1,3	2,3± 1,6	.333
Parite	1,5 ± 1,2	1,2± 0,8	.319
Gebelik haftası	38,5± 1,1	38,3± 2,1	.652
1. dakika Apgar skoru	8,5 ± 0,5	9 ± 1,5	**<0,001**
5. dakika Apgar skoru	9,5 ± 0,5	9,7± 1,5	**.002**
Doğum ağırlığı	3091,8 ± 519,9	3122,3± 464,1	.761
Doğum boyu	48,8 ± 2,4	49,3± 1,8	.313

Değerler ortalama +/- standart sapma olarak verildi.
Bağımsız T Testi uygulandı.

25-OH D vitamininin doğum ağırlığı, doğumdaki boy, maternal B12, ferritin, demir, folik asit, FL mm değerleri ile korelasyonu incelendiğinde; 25 OH D vitamin değeri ile ultrasonla ölçülen femur uzunluğu ve doğum boyu arasında anlamlı pozitif korelasyon olduğu tespit edilmiştir(sırasıyla p=0.020, p=0.050).

TARTIŞMA

Çalışmamızda antenatal bakım almayan Suriyeli sığınmacı gebelerin verilerini değerlendirerek maternal ve neonatal sonuçlarını çıkarmayı planladık. Yeterince antenatal bakım hizmeti alamayan sığınmacı gebelerin olumsuz maternal ve neonatal sonuçlar açısından risk altında olduğunu tespit ettik.

Doğum yapan kadınların %82'sinin, gebelik sırasında en azından bir kez doğum öncesi bakım aldığı tahmin edilmektedir (8). DSÖ asgari olarak gebelik sırasında dört kez ziyaret önerir ; ancak, çoğu yüksek gelirli ülkelerde, daha çok ziyaret standart olarak sunulmaktadır (9). Sanayileşmiş Batı ülkelerinde sağlık hizmetlerine geniş kapsamlı erişime rağmen, göçmen olmayan kadınlar ile karşılaştırıldığında gebelik sırasında daha az kontrole gitme eğiliminde oldukları tespit edilmiştir (10, 11). Sistematik bir derlemede, bu Batılı olmayan göçmen kadınlar arasında antenatal bakıma erişmede engelin en sık sebebinin dil yetersizliği ve sağlık sistemlerine ilişkin bilgi eksikliği olduğu tespit edilmiştir (12). Multiparite, plansız gebelik, doğum öncesi bakımın gereksiz olarak algılanması, sosyoekonomik sıkıntılar bireysel engel olarak değerlendirilmekle beraber belgesiz göçmenler için, yetki ve sigorta eksikliği sağlığa erişim için önemli engeller olarak bulunmuştur (13). Bir literatürde, Small ve ark. göçmen kadınların bakış açısından bakımla ilgili beklentilerini değerlendirmiş ve göçmen kadınların göçmen olmayan kadınlarla aynı düzeyde bakım almayı beklediklerini bulmuşlardır ancak, bu çalışmaya göre göçmen kadınlar beklentilerini daha az sıklıkta yerine getirilebilmişlerdir (14).

Mülteciler göç ettikleri ülke ne kadar güvenli olursa olsun sosyal, fiziksel ve psikolojik sorunlarla karşı karşıya kalmaktadır. Kadınlar ve çocuklar bu sorunlardan en çok etkilenen gruplardır. Özellikle erken-orta adölesan dönemdeki gebeliklerin artmış olumsuz gebelik sonuçları açısından riskli olduğu gösterilmiştir. Türkiye'de yapılan bir çalışmada genç yaştaki gebelerin antenatal bakım programlarına katılımlarının daha az olduğu gösterilmiştir (6). Daha önce yapılan bir çalışmada sığınmacı gebelerin yaş ortalaması 24, Erenel ve ark. nın yapmış olduğu başka bir çalışmada ise 25,2 olarak bulunmuştur (6, 15). Bizim çalışmamıza alınan gebelerin yaş ortalaması ise 23,9 idi. Eğitim düzeyi, sosyal yaşam ve din gibi çeşitli faktörler gebelik yaşını etkileyebilir. Bu durum savaş ortamından genç yaştaki kadınların daha çok etkilendiğinin göstergesi olabilir.

Çalışmalar göçmenlerdeki sezaryen doğum için en yaygın endikasyonların tekrarlayan sezeryan, doğum eyleminde ilerlemede başarısızlık / distosi, fetal sıkıntı ve baş-pelvis uyumsuzluğu (CPD) olduğunu göstermektedir (16, 17). Göçmen kadınlar arasında yüksek sezaryen oranlarını açıklamak için potansiyel katkıda bulunan bir çok faktör tespit edilmiştir; ancak kanıtlar yetersizdir (18). Bunlar göçmen kadınların fiziksel ve psikolojik sağlık, sosyal ve kültürel durumları ve maternal bakım kalitesini içermektedir. Alıcı ülkede kalınan süre ve göç sınıflandırılması da kadınların sezaryen riskini etkiliyor görünmektedir. Literatür araştırması göçmen kadınlarda preeklampsi ya da plasental komplikasyonlar gibi faktörler nedeniyle daha fazla sezaryen gerektiğine dair tutarlı bir kanıt olmadığını gösterdi. Bazıları, bulaşıcı hastalıklar veya anemi gibi diğer hastalıkların kadınların genel sağlık durumunda rol oynayabileceğini göstermektedir (17, 19). Biz çalışmamızda normal doğum oranını %67,8, sezaryen ile doğum oranını %32,2 olarak bulduk. sezaryen ile doğum yapan hastalar arasında en sık sezaryen endikasyonunun %11,9 oranla geçirilmiş sezaryen öyküsü olduğunu tespit ettik, akut fetal distres endikasyonunu %9,4, CPD endikasyonunu %3,5 olarak bulduk.

Farklı merkezlerden elde edilen raporlar mültecilerin kötü perinatal sonuçlara duyarlı olduğunu göstermiştir. Avrupalı olmayan göçmen grubunu araştıran, Belçika'dan bir analiz, Fas ve Türkiye'deki kadınlarda konjenital anomalilere bağlı perinatal mortalite riskinin yüksek olduğunu ortaya çıkardı (20). Literatürde, farklı yerli nüfuslar arasında yaşayan azınlıkların prenatal sonuçları arasında belirgin farklılıklar vardır. Bunlar; yüksek oranda düşük doğum ağırlığı, erken doğum, perinatal mortalite ve konjenital anomalilerdir (21). Biz de çalışmamızda konjenital anomali olan bebek oranını %5,5 olarak bulduk. Polistemi %1,5, nöral tüp defekti %0,5, hipoplastik sol kalp %0,5, duodenal atrezi %0,5, hidrosel %0,5, ambigius genitalya %0,5, anensefali %0,5, özefagus atrezi %0,5 oranında idi.

Göçmen kadınlar için özel risk faktörleri, olumsuz sosyoekonomik konum, akrabalık, izolasyon nedeniyle duygusal gerginlik ve düşmanlık ya da ayrımcılık konularını içermektedir (22). Halk sağlığı ve sağlık sistemine ilişkin çalışmalar, doğum öncesi erken aşamada antenatal bakımı, konjenital anomaliler için erken tarama yapılmasını, gebelik öncesi folik asit takviyesi ve akrabalık dahil olmak üzere ölü doğum ve konjenital anomali risk faktörleri hakkında bilgi verilmesini içermelidir.

Çalışmamızda ölçülen 25-OH D vitamini değeri ile ultrasonla ölçülen FL ve doğumdaki boy arasında pozitif yönde düşük düzeyde korelasyon tespit ettik. Ancak doğum ağırlığı ile 25-OH D vitamini arasında korelasyon izlemedik. Demir değeri normal ve düşük olanlar arasında yaş, gravida, parite, doğum haftası, doğum ağırlığı ve boy ortalaması açısından anlamlı fark saptanmaz iken, demir değeri düşük olanların Apgar 1 ve 5 skoru anlamlı olarak daha düşük bulduk. Gözlemsel çalışmalar gebelik öncesi ve perikonsepsiyonel vitamin ve mineral alımının düşük doğum ağırlığı ve / veya gestasyonel yaş için küçük (SGA) ve erken doğum riskinin azalması ile ilişkili olduğunu düşündürmektedir. Mevcut veriler gebeliğin ilk üç aylık döneminde ve öncesinde kadınlarda beslenmenin önemini göstermektedir (23).

Majör ve minör faktörlerin örneğin uyuşmayan dil ve suboptimal tercüman sistemi gibi sebeplerin yabancı uyruklu kadınlarla yetersiz iletişime neden olduğu gösterilmiştir. Bu durum yabancı uyruklu hastalarda danışma / sevkte gecikmelere, sağlık çalışanlarıyla yetersiz iletişime, yetersiz doğum öncesi bakıma neden olmaktadır (24).

Türkiye'deki sağlık politikası mültecilerin sağlık hizmetlerine ücretsiz erişimini sağlamaktadır. Türkiye'deki tüm gebeler gibi mülteci gebeler de doğum öncesi bakım kuruluşlarına ücretsiz olarak gidebilme hakkına sahiptir. Buna ek olarak gebelere vitamin ve demir takviyesi ücretsiz olarak verilmektedir. Düşük eğitim seviyesi ve antenatal bakımın önemiyle ilgili bilgi eksikliği sağlık kuruluşlarına yapılan başvuruları etkileyen önemli faktörlerdir(25). Gebelik ve doğum süresince yeterli bakım alınmamasına bağlı olarak gebelik komplikasyonları ve olumsuz neonatal sonuçlar sıklıkla görülmektedir. Sığınmacı bireylerin

özellikle genç ve reprodüktif dönemde olmaları bu durumun önemini arttırmaktadır. Yeterli bakım almayı teşvik etmek için olası faktörlerin iyi bilinmesi ve buna yönelik sağlık politikaları geliştirilmesi gerekmektedir.

Katılımcı sayısının görece yüksek olması ve laboratuvar parametrelerinin kapsamlı olması çalışmanın güçlü taraflarıdır. Çalışmanın kısıtlılıkları ise retrospektif dizaynı ve kontrol grubu olarak sağlıklı gebelerin alınmamasıdır.

SONUÇ

Halk sağlığı ve sağlık sistemine ilişkin çalışmalar, antenatal bakımı, konjenital anomaliler için erken tarama yapılmasını, gebelik öncesi folik asit takviyesi ve akrabalık dahil olmak üzere ölü doğum ve konjenital anomali risk faktörleri hakkında gençlere bilgi verilmesini içermelidir. Yüksek eğitim seviyesinin bireylerin antenatal bakım almada farkındalık geliştirmesine etki etmektedir. Eğitim seviyesi arttıkça kadınların dil engelini daha iyi çözümlemeleri sağlanacak buna bağlı olarak sağlık hizmetlerinden daha fazla yararlanma eğiliminde olacaklardır. Antenatal bakım almaya engel olan faktörlerin ortadan kaldırılması, böylece olumsuz gebelik ve doğum sonuçlarının önlenmesi hedeflenmelidir.

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Fetal Anomali Tanısı Almış Gebeliklerin Maternal Anksiyete ve Depresyon Düzeylerinin Değerlendirilmesi

Evaluation of Maternal Anxiety and Depression Levels in Pregnancies with Fetal Anomalies

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ÖZ

Amaç: Bu çalışmada intrauterin fetal anomali tanısı olan gebelerde depresyon ve anksiyete düzeylerinin objektif ölçüm envanterlerine dayalı olarak belgelenmesi, konu hakkında farkındalık yaratılması ve hastalara gerekli desteğin sağlanması amaçlandı.

Gereç ve Yöntem: Çalışma grubuna majör fetal anomali tanısı alan ve gebeliğinin devamına karar veren 18-41 yaş arası 40 gebe dahil edildi. Sağlıklı fetüsü olan benzer yaş aralığı ve gestasyonel haftadaki 40 gebe kontrol grubu olarak alındı. Gebelere Beck Depresyon Envanteri (BDÖ) ve Spielberger Durumluk-Sürekli Kaygı Envanteri (STAI) uygulandı.

Bulgular: İntrauterin fetal anomali tanısı alan gebeler ile kontrol grubu arasında anksiyete ve depresyon düzeyleri karşılaştırıldı. Ortalama BDÖ skoru çalışma grubunda anlamlı olarak daha yüksekti (P=0.008). STAI puanlamasında, durumluk kaygı düzeyi ortalaması (P□0.001) ve sürekli kaygı skoru ortalaması (P=0.001) çalışma grubunda kontrol grubuna göre istatistiksel olarak daha yüksek bulundu.

Sonuç: İntrauterin fetal anomalili gebelerin depresif semptom skorları ile durumluk ve sürekli kaygı düzeyleri sağlıklı gebelere göre artmıştır. Bu gebelere böyle bir zor dönemde profesyonel psikolojik destek ve gerekli tıbbi yardım sağlanmalıdır.

Anahtar kelimeler: Anksiyete, depresyon, fetal anomali, yüksek riskli gebelik

ABSTRACT

Aim: This study aimed to document depression and anxiety levels in pregnant women with intrauterine fetal anomalies based on objective measurement inventories, raise awareness of this issue and provide the necessary support to patients.

Materials and Method: Forty pregnant women between the ages of 18-41 who were diagnosed with a major fetal anomaly, and decided their pregnancy to continue were included in the study group. Forty pregnant women with a healthy fetus and gestational week and maternal age-matched with the study group were included as the control group. The Beck Depression Inventory (BDI) and the Spielberger State-Trait Anxiety Inventory (STAI) were applied to pregnant women.

Results: Anxiety and depression levels were compared between pregnant women diagnosed with an intrauterine fetal anomaly and the control group. The mean BDI score was significantly higher in the study group (P=0.008). In the STAI scoring, the mean state anxiety level (P□0.001) and the mean trait anxiety score (P=0.001) were found to be statistically higher in the study group compared to the control group.

Conclusion: The depressive symptom scores and the state and trait anxiety levels of pregnant women with the intrauterine fetal anomaly, increased compared to the healthy pregnant women. These pregnant women should be provided with professional psychological support and necessary medical assistance during this difficult period.

Keywords: anxiety, depression, fetal anomaly, high-risk pregnancy

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INTRODUCTION

While pregnancy is a desired and planned situation for many women, pregnancy is a physiological condition that also includes some risks for the mother and the infant. Pregnancy is a process in which there may be factors that can cause many anxiety and stress. Anxiety disorder is a psychiatric condition characterized by the continuous or intermittent intense and disturbing state of concern, distress, fear, and feelings of fear and anxiety during the day. Depression is a mood disorder with deep sadness, loss of interest in the environment, pessimistic thoughts, and an increased risk of suicide. It has been found that the frequency of anxiety and depression during pregnancy increases compared to the normal population (1). Depression is a common complication of pregnancy and the postpartum period. Maternal depression, anxiety, and stress are reported to be associated with preterm delivery, low birth weight, fetal growth retardation, and adverse fetal neurodevelopmental outcomes (2, 3). Factors such as the psychosocial status of the pregnant woman, socioeconomic condition, exposure to trauma, unplanned pregnancy, advanced age pregnancy, high-risk pregnancy, and the lack of social support are among the etiological causes (3).

The frequency of detecting major fetal congenital anomalies during pregnancy or the postpartum period is 2-3%. These anomalies generally include chromosomal or structural anomalies. Recently, the rate of intrauterine detection of fetal anomalies increases due to the development of antenatal screening tests and obstetric ultrasonography techniques. Some studies reported that women whose pregnancy has been terminated due to fetal anomaly experience significant emotional stress (4). There is also a systematic review stating that 20 to 100% of pregnant women with obstetric complications had increased levels of state anxiety, and high maternal anxiety levels might be associated with poor maternal outcomes (5). Pregnancy is a special period when the physical and mental health of the mother and fetus are closely related. It requires careful consideration of mental well-being while taking care of the physical health of the mother and the fetus. Pregnancies with fetal or maternal risk, adversely affect the antepartum and postpartum periods of patients and may even cause them to spend their reproductive years under psychological and physiological stress. This study aimed to determine depression and anxiety levels in pregnant women who continue their pregnancies with intrauterine fetal anomalies, raise awareness of this issue, and provide patients with the necessary support during the antenatal and postpartum periods.

MATERIALS AND METHOD

Study Design

This study was designed as a prospective case-control study.

Participants

Forty pregnant women between the ages of 18-41 who presented to Ankara City Hospital Perinatology outpatient clinic which is a tertiary referral center, between January 2022 and April 2022, were diagnosed with major fetal anomalies during their antenatal follow-ups (congenital heart disease, central nervous system anomaly, chromosomal anomaly), were in the second and third trimesters of their pregnancy, were included in this case-control study. Fetal anomaly diagnosis was confirmed by ultrasonographic anomaly screening or an invasive prenatal diagnostic test (amniocentesis, CVS, cordocentesis). Pregnant women who wanted to continue their pregnancy were included in the study group. Their diagnoses were categorized as structural multiple malformations (40%), central nervous system anomalies (25%), congenital heart anomalies (27.5%), and chromosomal anomalies (7.5%). We could not include first-trimester pregnancies in the study, because of waiting for invasive prenatal test results and waiting 4 weeks after diagnosis to apply the questionnaires. Forty pregnant women with a singleton pregnancy who presented to the antenatal outpatient clinic for routine check-ups did not have any chronic disease or suspected fetal anomaly and were in the same age range and gestational week were included as the control group. Pregnant women who did not volunteer to participate in the study had a diagnosis of mental illness, and had a chronic or pregnancy-related systemic disease were excluded from the study. The study protocol was approved by the Ministry of Health of the Republic of Turkey and was performed in line with the Declaration of Helsinki. The ethics committee approval was obtained from Ankara City Hospital No. 2 clinical research ethics board with the decision number E2-22-1261 and dated 19/01/2022. All study participants were informed and their consent was obtained.

Data collection

The age, height, weight, education and employment status, monthly income level, history of smoking and alcohol use, and sociodemographic characteristics of the patients who volunteered to participate in the study were recorded. The number of pregnancies, the history of miscarriage, the number of living children, whether the pregnancy was planned or not, the history of a fetal anomaly in previous pregnancies, and kinship with the spouse were questioned and recorded. The form of the detected fetal anomaly was examined and classified. Obstetric ultrasonographic examinations of all patients were performed. The case follow-up form was prepared and filled out separately for both groups. The Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) were applied to pregnant women. These questionnaires were applied to pregnant women in the study group 4 weeks after the diagnosis of a fetal anomaly to rule out possible symptoms related to an acute stress reaction.

Study Instruments

Beck Depression Inventory (BDI): It is a depression rating scale consisting of 21 questions, which was developed by Aaron T. Beck in 1961 and revised in 1996, and whose validity and reliability study was conducted in Turkey by Hisli et al. (6). By the score ranges corresponding to the patient's answers, the scale is rated as minimal depressive symptoms between 0-9 points, mild depressive symptoms between 10-16 points, moderate depressive symptoms between 17-29 points, and severe depressive symptoms between 30-63 points.

State-Trait Anxiety Inventory (STAI): Its original form was developed by Charles Spielberger et al. and revised over the years. It was adapted to Turkey by Öner and LeCompte (7). Individuals respond to each 20-item scale with the instruction of how he/she "usually" feels. The STAI has two types of statements. Direct statements express negative emotions, and reversed statements express positive emotions. After the total weights of

the direct and reversed statements are found separately, the total weight score of the reversed statements is subtracted from the total weight score obtained for the direct statements. Scores range from 20 (low anxiety) to 80 (high anxiety). High scores indicate high anxiety levels and low scores indicate low anxiety levels. The State Anxiety Inventory (SAI) is used to evaluate reactions due to sudden excitement. The Trait Anxiety Inventory (TAI) is a sensitive scale used to measure the continuity of anxiety experienced by a person.

Statistical analysis

Statistical analyses were performed using IBM SPSS for Microsoft Windows 25.0 (SPSS Inc., Chicago, IL, USA). For categorical variables, frequency (n) and percentage (%), and for numerical variables, mean (X) and standard deviation (sd) statistics were calculated. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test). Descriptive analyses were given using the mean and standard deviations for normally distributed variables. Independent groups were compared using the Student's t-test. The ratios among independent groups were given using the chi-squared test and cross tables. Cases with a p-value less than 0.05 were considered statistically significant results. Correlation coefficients and statistical significance were calculated with Spearman's test for the relationships between the non-normally distributed variables. Type-1 error level was used as 5% for statistical significance.

RESULTS

Sociodemographic characteristics were compared between the study and control groups. Considering the educational status, the educational level was found to be similar between the groups (P=0.479). It was observed that the pregnant group with fetal anomaly mostly consisted of multiparous pregnant women by 67.5% (27/40), while the control group mostly consisted of primiparous pregnant women by 57.5% (23/40). This result was a statistically significant difference (P=0.004). When the case group was compared with the control group, it was observed that pregnant women constituting the case group contributed statistically less to their working life (P=0.032). There was no difference between the groups in terms of consanguineous marriage (P=1.0) and the history of abortus (P=0.655). However, when the history of infants with an anomaly was examined, it was determined that there was a history of infants with an anomaly at a level that would cause a statistically significant difference in the group with intrauterine fetal anomaly (P=0.040). The mean age between the groups was similar by 28.67±6.33 in the case group and 26.55±5.57 in the control group (P=0.115), and there was no difference in monthly income level (P=0.584) (Table 1).

Table 1. The intergroup comparison of sociodemographic characteristics

		Fetal anomaly group N:40 n (%)	Control group N:40 n (%)	P value
Education N (%)				0.479[a]
	illiterate	1 (2.5%)	1 (2.5%)	
	primary	14 (35%)	8 (20%)	
	High school	16 (40%)	18 (45%)	
	University and above	9 (22.5%)	13 (32.5%)	
Parity N (%)				**0.004[a]**
	primiparity	13 (32.5%)	23 (57.5%)	
	multiparity	27 (67.5%)	17 (42.5%)	
Employment Status N (%)				**0.032[a]**
	employed	5 (12.5%)	13 (32.5%)	
	housewife	35 (87%)	27 (67.5%)	
Consanguineous Marriage N (%)				1.00[a]
	yes	9 (22.5%)	9 (22.5%)	
	no	31 (77.5%)	31 (77.5%)	
Previous fetal anomaly history N (%)				**0.040[a]**
	yes	4 (%10)	0 (0%)	
	no	36 (90%)	40 (100%)	
Abortion history N (%)				0.655[a]
	yes	9 (22.5%)	12 (30%)	
	no	31 (77.5%)	28 (70%)	
Monthly** income N (%)				0.584[a]
	1*	20 (50%)	18 (45%)	
	2*	15 (37.5%)	19 (47.5%)	
	3*	5 (12.5%)	3 (7.5%)	
Age Mean±std.				0.115[b]
		28.67±6.33	26.55±5.57	

** Prepared according to the data of TurkStat on June 15, 2021 (22).

*1= minimum wage and below income, 2= income between minimum wage and poverty threshold, 3= income above the poverty threshold. Bold values indicate statistical significance at the p<0.005 level. [a] Chi-squared test; [b] Student's T-test.

The BDI score was found to be statistically significantly higher in the pregnant group with a diagnosis of a fetal anomaly compared to the control group (P=0.008). While the mean score was compatible with minimal depressive symptoms by 8.17 6.34 (28/40 70%) in the control group, it was found to be compatible with mild depressive symptoms by 12.42 7.59 (16/40 40%) in the pregnant group with fetal anomaly (P=0.008). In the STAI scoring, state anxiety (P=0.000) and trait anxiety (P=0.001) scores were found to be statistically significantly different from the control group (Table 2).

Table 2. The intergroup comparison of the BDI, STAI-S, STAI-T inventories

	Fetal anomaly group mean ±std.	Control group mean ±std.	P value[b]
BDI score	12.42±7.59	8.17±6.34	**0.008**
STAI-S score	50.65±10.03	35.95±9.97	**0.000**
STAI-T score	46.00±7.93	39.90±7.70	**0.001**
Total	40	40	

BDI: Beck Depression Inventory; STAI-S: State-Trait Anxiety Inventory-State; STAI-T: State-Trait Anxiety Inventory- Trait. Bold values indicate statistical significance at the p<0.005 level. [b] Student's T-test.

The correlation between the patients' sociodemographic characteristics and their anxiety and depression states was examined. There was a positive correlation between the state anxiety level and the patient's age and gravity. It was determined that the state anxiety scores of the patients increased as their age increased (P=0.036) and the state anxiety levels of the patients increased as gravity increased (P=0.034). No correlation was found between educational status, gestational week, and anxiety and depression scores (Table 3).

Table 3. Correlation of sociodemographic characteristics with anxiety, depression, and stress states

	BDI score		STAI-S score		STAI-T score	
	r	p	r	P	r	p
Age	0.138	0.224	0.235	**0.036**	-0.018	0.876
Gestational Age	0.063	0.580	0.082	0.470	-0.015	0.895
Education	-0.108	0.340	-0.131	0.246	-0.199	0.078
Gravida	0.167	0.140	0.237	**0.034**	0.102	0.366

BDI: Beck Depression Inventory; STAI-S: State-Trait Anxiety Inventory-State; STAI-T: State-TraitAnxiety Inventory- Trait. Bold values indicate statistical significance at the p<0.005 level. Spearman's correlation test.

Depression and anxiety scores between the second and third trimesters were compared in the study group. There was no difference in depression score and trait anxiety level. However, the state anxiety level was significantly higher in the third trimester of pregnancy compared to the second trimester (P=0.018) (Table 4).

Table 4. Depression and anxiety levels between the trimesters

	Second trimester Mean±std. N:22/40 (55%)	Third trimester Mean±std. N:18/40 (45%)	P value[b]
BDI score	10.77±4.47	14.44±9.99	0.130
STAI-S score	47.31±9.17	54.72±9.76	**0.018**
STAI-T score	45.27±6.53	46.88±9.49	0.528

BDI: Beck Depression Inventory; STAI-S: State-Trait Anxiety Inventory-State; STAI-T: State-Trait Anxiety Inventory- Trait. Bold values indicate statistical significance at the p<0.005 level. [b] Student's T-test.

DISCUSSION

This study aimed to compare the depression and anxiety levels of pregnant women diagnosed with intrauterine fetal anomaly and pregnant women with healthy fetuses. The present study showed that depression, state, and trait anxiety levels of pregnant women diagnosed with intrauterine fetal anomaly increased compared to pregnant women with healthy fetuses.

According to the present study, carrying a fetus with an anomaly was found to be associated with an increased level of anxiety during pregnancy. This result is consistent with previous studies (8-10). One of these studies was based on retrospective reporting and children included in the study follow-up to three years old. These points were different from the present study (8). According to the results of the survey conducted 6 weeks after the termination, it was observed that more post-traumatic stress symptoms occurred in women who had a pregnancy termination in the second trimester due to fetal anomaly compared to first-trimester terminations. This study reported that state anxiety levels were higher in pregnant women with a diagnosis of fetal anomaly requiring surgery in the neonatal period 6 weeks after termination compared to pregnant women with a healthy fetus (10). In this study, questionnaires were applied to the individuals just after the diagnosis. In the present study, we applied the tests 4 weeks after the diagnosis of a fetal anomaly to rule out possible symptoms related to an acute stress reaction. A study indicated that undergoing a prenatal screening test independently of the diagnosis of fetal anomaly did not affect the level of anxiety, but pregnant women with a positive screening test result had higher state anxiety levels (11). In another study, the anxiety levels of 60 pregnant women with positive biochemical Trisomy 21 screening results before and after the amniocentesis procedure were measured, and it was observed that the state anxiety levels of patients increased significantly more during the waiting period for karyotype results (12).

The incidence of antenatal depression is considered to vary between 7 and 19% (13, 14). Another important result of the present study was that the diagnosis of the fetal anomaly was associated with increased depression symptoms in pregnant women. We found only one study evaluating the relationship between the diagnosis of fetal anomaly and depressive symptoms during pregnancy. Similar to the results of our study, it revealed that the diagnosis of the fetal anomaly was associated with increased depressive symptoms and increased anxiety, and depression symptoms also continued after delivery (8).

Studies evaluating anxiety and depression levels between the trimesters of pregnancy have reported that depression and anxiety scores are higher in the third trimester compared to other trimesters (15, 16). Another study reported that anxiety levels were high in the first and third trimesters during pregnancy, and depressive symptoms were high in the first trimester and gradually decreased in the following trimesters (17). Our study observed that the state anxiety levels of pregnant women with a fetal anomaly in the third trimester were higher than those in the second trimester. Higher anxiety levels in the third trimester of pregnancy may be explained by the fact that the upcoming childbirth and/or the anticipations about being a parent. To face with an unknown situation about the condition of the fetus could be one of the possible reasons. Further research should be carried out to clarify this finding. The present study demonstrated a positive correlation between maternal age, parity, and state anxiety levels in pregnant women with a diagnosis of intrauterine fetal anomaly. This result is different from the results of some studies in the literature. Contrary to our results, some studies evaluating the relationship between maternal age and anxiety level in pregnant women associated young maternal age with increased anxiety levels during pregnancy (18-20). But, these studies evaluated only healthy pregnant women. On the other hand, it was reported that advanced age was associated with increased depression and anxiety symptoms in women who continued their pregnancy with a diagnosis of a fetal anomaly as in our study (8, 10). When evaluated with the studies in the literature, the result of our study may be useful in identifying high-risk groups and receiving the necessary support in the early period.

There are studies indicating that low educational level and socioeconomic level, insufficient social support, early gestational age, and first pregnancy are risk factors for the diagnoses of anxiety disorders and depression in pregnancy (17, 18, 21). No significant difference was identified between the two groups included in our study in terms of age, educational level, and monthly income levels. Only the difference between the groups in terms of parity numbers was significant.The small sample size is one of the major limitations of the study. The small sample size may have limited the generalizability of the study results by causing low statistical power. Fetal anomaly diagnoses were not confirmed in the postnatal period. Furthermore, the fact that the postpartum period and spouse anxiety and depression levels were not included in the evaluation can be considered among the other limitations.

CONCLUSION

In conclusion, diagnosis of a fetal anomaly is almost always an unexpected and difficult situation to cope with for pregnant women and increases the risk of depression and anxiety in expectant mothers during pregnancy. Considering these factors and the physiology of pregnancy, mood and anxiety disorders in expectant mothers within high-risk fetal situations should be addressed carefully, and an attempt should be made to provide patients with maximum benefits through a multidisciplinary approach. Emotional state screening in the prenatal period among high-risk pregnancies may help physicians better identify the potential psychological distress. The early and accurate identification of pregnant women at risk, is critically important for providing adequate professional psychological support at the time.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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Abbreviations

BDI: Beck Depression Inventory

STAI: State-Trait Anxiety Inventory

CVS: Chorion Villus Sampling

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Evaluation of first trimester uterine artery resistance and placental volume in patients who had coronavirus disease-19 Before pregnancy

Gebelikten önce COVID-19 geçirenlerde ilk trimester uterine arter direnci, plasental volüm ve gebelik sonuçlarının incelenmesi

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ÖZ

Amaç: Gebelikte geçirilen koronavirüs hastalığı 2019 (COVID-19) vasküler hasar yaratarak ve uterin kanlanmayı etkliyerek gebelik sonuçlarını kötüleştirdiğine dair çalışmalar mevcuttur. Bu çalışmada Covid-19 geçirdikten sonra gebe kalanlarda ilk trimester plasenta gelişimini ve gebelik sonuçlarını değerlendirerek ve Covid-19 etkisinin kalıcılığını araştırdık.

Gereçler ve Yöntem: Bu prospektif çalışma, gebeliğinden bir yıl öncesine kadar Covid-19 maruziyeti olan gebeler ile sağlıklı gebe kontrol grubundaki plasental hacim ve uterin arter Doppler akım ölçümleri arasındaki farklılıkları değerlendirmektedir.

Bulgular: Yaş, doğum oranı ve vücut kitle indeksi gibi demografik özelliklerin, 50 hasta ve 50 kontrol üzerinde yapılan bu çalışmada benzer olduğu görüldü. Oligohidramniyoz, prematürite, preeklampsi ve intrauterin büyüme geriliği gibi çeşitli sonuçlar incelendiğinde; bu verilerde istatistiksel olarak anlamlı olmayan hafif varyasyonlar dikkat çekti. Doğum ağırlığı ve 1. dakika Apgar skoru gibi parametreler iki grup arasında benzerlik gösterirken, plasental hacim ve uterin arter Doppler sonuçlarında anlamlı farklılıklar saptanmadı.

Sonuç: Yapılan çalışmada, gruplar arasında plasental veya Doppler ölçümlerinde herhangi bir farklılık bulunmamıştır. Bugüne kadar yapılan çalışmalar genellikle gebelikte geçirilen Covid -19'un gebelikteki etkisi üzerine gerçekleştirilmiştir. Bu çalışma ise gebelik öncesi geçirilen Covid-19'un gebelikteki etkisinin belirlenmesine yardımcı olmuştur.

ABSTRACT

Aim: There are studies showing that acquiring coronavirus disease 2019 (COVID-19) while pregnant might cause vascular damage, affect uterine blood circulation, and worsen pregnancy outcomes. In this study, we looked at the first-trimester placental development and pregnancy outcomes in people who conceived after getting better from Covid-19. We also looked into the durability of the Covid-19's effects on pregnancy.

Matherials and Methods: This prospective case-control study investigates placental volume and uterine artery Doppler flow differences in pregnant women with Covid-19 exposure within a year prior to pregnancy versus healthy pregnant controls.

Results: In a study involving 50 patients and 50 controls, it was discovered that demographic traits like age, birth rate, and body mass index were comparable. There were statistically insignificant slight differences in these results when different outcomes, including as oligohydramnios, preterm, preeclampsia, and intrauterine growth retardation, were studied. While birth weight revealed similarity between the two groups, placental volume and uterine artery Doppler results did not reveal any appreciable variations.

Conclusion: No distinction between the groups' placental or Doppler readings was found in the investigation that was completed. This work has helped identify the impacts of Covid-19 contracted prior to pregnancy on gestation, whereas previous study has mainly focused on the impact of Covid-19 infected during pregnancy.

Keywords: Intrauterine growth retardation, placental volume, preeclampsia, uterine artery Doppler

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INTRODUCTION

Placental volume is a structure that grows as a result of increased vascularity with the effect of hormones secreted by the placenta during pregnancy. Placental volume plays an important role in fetal development and varies in the prenatal period (1). Ultrasonographic methods are the most common technique used to measure placental volume. This method can be performed at any time of pregnancy and can measure placental volüme (2). Placental volume can be calculated by creating a three-dimensional image, or placental thickness, width, and length can be measured using a two-dimensional image. Evaluation of placental volume plays an important role in determining complications in pregnancy (3). Placental volume may be decreased in cases such as placenta previa, placental abruption, and growth restriction. On the other hand, placental volume may increase in gestational diabetes and twin pregnancies. Ultrasonographic evaluation of placental volume plays an important role in pregnancy follow-up and provides information about the health of the fetus (4,5). The effect of coronavirus disease 2019 (Covid-19) infection on placental volume is not fully known. However, some studies show that Covid-19 infection may cause a decrease in placental volume in late pregnancy (6). There are not enough studies yet on whether having Covid-19 has any effect on uterine artery pulsatility index (PI) dopplers. However, Covid-19 infection, like other viral infections, can cause vascular damage and therefore affect blood flow in the uterine arteries (7).

Covid-19 can create detrimental effects on the placenta, potentially leading to malperfusion and resulting in adverse outcomes (8). Understanding the long-term effects of these impacts and how they affect subsequent pregnancies is of significant importance. The primary objective of this study is to determine the persistence of Covid-19-induced detrimental effects on the placenta and their impact on subsequent pregnancies.

MATERIALS AND METHOD

Study Design and Patients' Selection

Our study was designed as a prospective case-control study aiming to evaluate the differences in placental volume and uterine artery Doppler flow between pregnant women who had contracted Covid-19 within the past year before pregnancy and healthy pregnant women. There is also assessed pregnancy outcomes. The study commenced after obtaining ethical committee approval (decision no.15-02-2022- 2022/02-44). The inclusion criteria for our study consisted of women who presented for the first-trimester screening test and had a gestational age of between 12 and 14 weeks of pregnancy, determined based on the last menstrual period. Only women with singleton pregnancies and no additional medical conditions were included. In the patient group, 50 pregnant women who had tested positive for Covid-19 by PCR prior to pregnancy within the last year were recruited. The control group comprised 50 pregnant women who had not previously contracted Covid-19 (no symptoms and negative PCR results). Placental volume and uterine artery Doppler measurements were conducted for each participant. Exclusion criteria encompassed multiple pregnancy, molar pregnancy, cesarean scar pregnancy, ectopic pregnancy, maternal systemic diseases, and cases of fetal demise. The findings of PCR tests were taken into consideration for the individuals hired for work, and vaccination records were not questioned.

Perinatal complications such as oligohydramnios, preeclampsia, fetal growth restriction, and preterm delivery were documented during the patients' prenatal follow-up.

Using sonographic measurements of intrauterine growth retardation (IUGR), such as fetal biparietal diameter, head circumference, abdominal circumference, and femur length, the estimated fetal weight (EFW) was characterized as falling below the 3rd percentile, accompanied by the observation of diastolic end-flow loss during Doppler examination. Furthermore, the EFW percentile was ascertained based on the 'International estimated fetal weight standards of the INTERGROWTH-21st Project' study (9).

Oligohydramnios was characterized based on the definitions provided by Rabie et al. as an amniotic fluid index (AFI) measurement below 5% or less than 5cm, along with a single deepest pocket (SDP) measurement of 2 cm or less (10).

In our study, the diagnosis of preeclampsia for our patients was based on the diagnostic criteria provided by the American College of Obstetricians and Gynecologists (ACOG) (11).

Ultrasound Measurement Techniques of The Placenta

The US measurements were conducted by a single sonographer with 10 years of experience using the Samsung Ultrasound System HS70A, a 3D ultrasound machine manufactured by Samsung Medison Company in the Republic of Korea. The 3D ultrasound probe was utilized to determine the location and maximum vertical diameter of the placenta. Subsequently, the placental contour was manually recorded in 6 consecutive images to ensure exclusion of the uterine wall. The placental volume was automatically calculated for all planes using the Virtual Organ Computer-Aided Analysis (VOCAL) technique.

Statistical Analysis

All statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) v.23.0 for Windows (SPSS, Inc., Chicago, IL, USA). Categorical variables were presented as numbers and percentages, and continuous variables as mean, deviation, and minimum–maximum. Pearson's Chi-square test was used to compare categorical variables. For comparing continuous variables between the groups, independent Student's t-test was used for binary variables by controlling the distributions. The differences observed between the groups were summarized using a boxplot. The statistical significance level was set at P:0.05 for all the tests.

RESULTS

We aimed to prospectively compare the effect of having Covid-19 in the last 1 year on placental volume and uterine artery Doppler flows between 2 groups, 50 patients in the study group and 50 patients in the control group. The mean age was 25.3(±5.4) in the Pregnant with Previous Covid-19 group and 24.4 (±5.5) in the control group (p=0.4). When compared in terms of the number of births, the mean of the study group was 2.8(±1.2) while it was 2.9(±1.4) in the control group (p=0.7). When the body mass index was compared between the 2 groups, it was found to be 27.3(±3.8) in the study group and 27.6(±4.3) in the control group (p=0,6) (Table 1).

Table 1: Comparison of Clinical and Obstetric Outcomes

	Pregnant with Previous COVID-19 patient (n=50)	Control patient (n=50)	P Value
Age	25.3(±5.4)	24.4(±5.5)	0.4
Gravide	2.8(± 1.2)	2.9(±1.4)	0.7
Body Mass Index	27.3(±3.8)	27.6(±4.3)	0.6
Preterm Birth			
Yes	5 (%10)	4(%8)	0.77
No	45(%90)	46(%92)	
Oligohidroamniyozis			
Yes	6 (%12)	7(%14)	0.76
No	44(%88)	43(%86)	
İntra Uterin Growth Restriction			
Yes			0.5
No	7(%14)	9(%18)	
	43(%86)	41(%82)	
Preeclampsia			
Yes	3(%6)	2(%4)	0.5
No	47(%94)	46(%96)	

We compared the frequencies of intrauterine growth retardation, oligohydramnios preterm birth and preeclampsia parameters between the two groups. While oligohydramnios was seen in 6 (12%) patients in the group that had Covid-19 infection, amniotic fluid was normal in 44 (88%) patients. In the control group, while oligo was detected in 7 (14%) patients, amniotic fluid was normal in 43 (86%) patients. (p=0,76) While intrauterine growth retardation was observed in 7 (14%) patients in patients who had Covid-19, it was not detected in 43 (86%) patients. In the control group, while iugr was detected in 9 (18%) patients, it was not detected in 41 (82%) patients.(p=0,5) When the 2 groups were compared, preterm birth was seen in 5 (10%) patients in the study group, while 45 (90%) patients had term births. In the control group, 4 (8%) patients had petterm birth, while 46 (92%) patients had term births. (p=0.77) While preeclampsia was seen in 3 (6%) patients in the Pregnant with Previous Covid-19 group, it was not detected in 47 (94%) patients. In the control group, preeclampsia was observed in 2 (4%) patients (p=0.5) (Table1).

When the group with placental volume Covid-19 was compared and the control group, 60,7 ml (± 4,97) was found in the Pregnant with Previous Covid-19 group and 62,7 ml (±5,34) in the control group. No significant difference was observed between the two groups. There was no statistically significant difference between the mean uterine artery PI parameters for the 2 groups. Mean uterine artery PI was found to be 1.79 (±0.23) in the Pregnant with Previous Covid-19 group, and 1.70 (±0.14) in the control group. Birth weight was 3065 g (±901) in the Pregnant with Previous Covid-19 group and 2983 (±490) in the control group (p=0.5). There was no statistically significant difference between the 2 groups (Table2).

Table 2: Comparison of perinatal and neonatal effects of having COVID 19 infection

	Pregnant with Previous COVID-19 patient (n=50)	Control patient (n=50)	P Value
Placenta volüme(ml)	60.7 (± 4.97)	62.7 (±5.34)	0.053
Mean UA Artery PI	1.79 (±0.23)	1.70 (±0.14)	0.09
Birth Weight	3065 (±901)	2983 (±490)	0.5

DISCUSSION

Uterine artery Doppler measurement is performed to assess the blood flow in maternal uterine arteries. Normal blood perfusion in the uterus is of vital importance for supporting fetal development and placental function. Spiral arterioles that supply the intervillous space in the placenta undergo significant morphological changes to meet the increasing demands of the fetoplacental unit (12). Alterations in these changes may result from defective placentation and contribute to the development of conditions such as preeclampsia and fetal growth restriction (13).

Understanding the relationship between uterine artery blood flow and placental development is fundamental in comprehending the normal placental process and its disruption in conditions like preeclampsia and fetal growth restriction (12).

The existing literature provides diverse findings regarding the impact of Covid-19 on uterine artery Doppler parameters. A majority of these studies indicate a negative effect of the Covid-19 virus on placentation, resulting in detrimental alterations in fetal Doppler parameters (14,15). The mean uterine artery pulsatility index (PI) in the group of pregnant women with a previous Covid-19 infection was 1.79 (±0.23), demonstrating a higher value compared to the control group with a mean of 1.70 (±0.14). However, upon statistical analysis, no significant difference was found between the two groups in terms of the mean uterine artery PI.

During pregnancy, changes in the immune system such as a shift from T-helper 1 (Th1) to Th2 response, decreased natural killer (NK) cell population, and reduced plasmacytoid dendritic cells can be observed. Additionally, there is an increase in progesterone levels, which plays a regulatory role in the circulating immune system, and alterations in pattern Toll-like receptors (TLRs) may occur. These alterations can impact the immune response against viral infections during pregnancy, but further research is needed to determine their precise effects on Covid-19 (16). First-trimester miscarriages occur in approximately 10-15% of pregnancies and can stem from genetic, environmental, or multifactorial etiologies. Mid-trimester pregnancy losses, with an estimated incidence rate of 1-2%, are thought to be influenced by maternal general conditions and a heterogeneous array of causes (17).

In a study conducted by Kazemi et al. (17), it was postulated that Covid-19 cases might be associated with placental insufficiency and inflammation, potentially contributing to pregnancy losses and preterm birth. Nevertheless, Ryan et al (18). Underscored the insufficiency of evidence to establish a definitive relationship between preterm birth and Covid-19 infection, notwithstanding the occurrence of cases involving spontaneous preterm membrane rupture.

According to the cohort study conducted by Pasternak et al. in Denmark, it was observed that Covid-19 was associated with an increased frequency of preterm birth (19). However, in our study, we did not find any statistically significant difference in terms of preterm birth between the control group and the patient group, which is consistent with previous studies in the literatüre (18,20).

Evidence suggests that Covid-19 can elicit inflammation at the maternal-fetal interface, potentially disrupting placental function and contributing to fetal growth restriction (FGR) and villitis (21).

Meta-analyses examining the relationship between Covid-19 and fetal growth restriction have demonstrated an association between Covid-19 infection during pregnancy and an increased frequency of intrauterine growth retardation (17,22). In the PAN-COVID study, which involved the evaluation of 8239 patients, it was observed that women who gave birth two weeks after contracting Covid-19 exhibited a significantly higher prevalence of fetal growth restriction compared to those who gave birth within the same two-week period of infection. However, the study did not yield statistically significant findings regarding fetal growth restriction (FGR) (20).

Despite the hypothesis that SARS-CoV-2 could lead to preeclampsia by binding to angiotensin converting enzyme 2 receptors and causing disruption in the renin-angiotensin system along with vasoconstriction, the precise underlying mechanism remains incompletely understood (23). In the study conducted by Wei et al., it has been demonstrated that Covid-19 is associated with preeclampsia (24). However, our study did not provide statistically significant evidence indicating an increased incidence of preeclampsia among individuals with a history of infection prior to pregnancy.

Covid-19 infection may be associated with many pregnancy complications such as early pregnancy loss, intrauterine growth retardation, preeclampsia (25). When these pregnant women were compared with the control group, no statistically significant difference was found in terms of the frequency of oligohydramnios.

In the literature, a correlation has been established between placental volume and pregnancy complications such as growth retardation, preeclampsia, and chromosomal anomalies (26–28). Considering the detrimental impact of the Covid-19 virus on placentation, our study aimed to investigate potential disparities in placental volume between pregnant women with a history of Covid-19 infection and a control group. The placental volume was determined as 60,7 ml (± 4,97) in the patient group, while it measured 62,7 ml (±5,34) in the control group, indicating a slightly higher value in the control group. However, this difference did not reach statistical significance, suggesting that there was no significant disparity in placental volume between the two groups.

There are many publications in the literature on Covid-19 and pregnancy outcomes. However, the effects of the history of Covid-19 infection on the next pregnancy need new research. While determining the method of our study, we planned to prospectively compare pregnant women who had Covid-19 infection in the last 1 year pre-pregnancy compared to the control group in terms of pregnancy complications. We found no difference between the two groups in terms of pregnancy complications. Although the placental volume seemed to be slightly lower in the pregnant with previous Covid-19 group, no statistically significant difference was found. In our view, the results obtained from this study can enhance our limited knowledge regarding the presence of permanent damage in pregnant women who have experienced Covid-19 pre-pregnancy.

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The Effect of Unreliable Social Media Use on Preoperative Cesarean Anxiety

Güvenilir Olmayan Sosyal Medya Kullanımının Ameliyat Öncesi Sezaryen Anksiyetesine Etkisi

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ÖZ

Amaç: Günümüzde birçok hasta sosyal platformları kullanarak sezaryen hakkındaki kişisel deneyimlerini ve görüşlerini paylaşmaktadır. Popüler bir fenomen olmasına rağmen, bu paylaşımların güvenilirliği ve hastanın anksiyetesi üzerindeki etkisi hakkında çok az şey bilinmektedir. Bu çalışmada, amacımız literatürde ilk olarak, sosyal medya kullanımının, hastaların ameliyat öncesi sezaryen anksiyetesi düzeylerine etkisini araştırmaktır.

Gereç ve Yöntem: Etik kurulun onayıyla, elektif sezaryen öncesi görülen 250 gebe çevrimiçi platformların kullanımıyla ilgili prospektif, tek merkezli bir anketi ve ayrıca ameliyat öncesi kaygı düzeyleri için Amsterdam Ameliyat Öncesi Kaygı ve Bilgi Ölçeğini (APAIS) doldurmaları istenmiştir.

Bulgular: 205 hasta anketi cevaplamıştır ve hastaların %98,8'i internet kullanıcısıdır. Ayrıca makale okuyanların %72,9'u ve video izleyenlerin %58,3'ü sezaryen için genel anestezi istemediklerini belirtmişlerdir. İnternette sezaryen anestezisi ile ilgili makale okuyanların ve video izleyenlerin APAIS anksiyete skorları daha yüksek bulunmuştur. Anestezi ile ilgili anksiyete cerrahi ile ilgili anksiyeteden anlamlı olarak daha yüksektir. Bu çalışma literatürde sosyal medyanın anksiyete üzerindeki etkisini değerlendiren ilk çalışmadır.

Sonuç: Bu çalışmada gebelerin yüksek oranda sosyal medya kullandığı ve güvenilirliği kontrol edilemeyen sosyal medya kullanımının hastaların anksiyete düzeylerini artırıcı etkisi olduğu gösterilmiştir.

Anahtar kelimeler: Anksiyete, sezaryen, internet, APAİS, rejyonel anestezi

ABSTRACT

Aim: Nowadays, many patients use social platforms to share their personal experiences and opinions about caesarean section. Despite being a popular phenomenon, little is known about the reliability of these posts and their impact on patient anxiety. In this study, our aim was to investigate, for the first time in the literature, the effect of social media use on patients' preoperative caesarean section anxiety levels.

Method: With the approval of the ethics committee, 250 pregnant patients seen before an elective caesarean section were asked to complete a prospective, monocentric questionnaire about the use of online platforms and also to complete the Amsterdam Preoperative Anxiety and Information Scale (APAIS) for preoperative anxiety levels.

Results: 205 patients answered the questionnaire and 98.8% of the patients were internet users. Also 72.9% of those who read articles and 58.3% of those who watched videos stated that they did not want general anaesthesia for caesarean section. APAIS anxiety scores of those who read articles and watches videos about caesarean section anaesthesia on the internet were higher and anaesthesia-related anxiety was significantly higher than surgery-related anxiety. This is the first study which evaluated the social media effect on the anxiety in the literature.

Conclusion: The findings show that pregnant women use social media extensively and that the use of social media, the reliability of which cannot be controlled, has an increasing effect on patients' anxiety levels.

Keywords: Anxiety, cesarian-sectio, internet, APAIS, regional anesthesia

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INTRODUCTION

Internet-based health information comes from a wide variety of sources. It can be highly specialised, as recently demonstrated in the field of regional anaesthesia, or easily accessible, such as social media, which provide information or services by enabling users to connect with others who share their interests or goals. (1) Social networks such as YouTube, Instagram, Tweeter or the others are not only a storage of videos but also a popular social network where users can interact and socialise (e.g. commenting, favouriting and following). Participating in communities and forums, blogging or tweeting are some of the activities of the so-called "ePatient", individuals who are "equipped, enabled, empowered and engaged in their health and health care decisions" (2).Especially after COVID-19, ePatients have started to share online videos about their health or medical problems, which seems to be partly driven by the inability of contemporary medical practice to meet patients' needs that go beyond the traditional treatment they receive, a trait also identified by participants in online health care groups. (3)

Anxiety is defined as a transient emotional state of unpleasant feelings of tension, apprehension, nervousness and fear, and high autonomic nervous system activity (4). Patients feel nervous or worried that something might happen, most commonly during the perioperative and postoperative periods, and affects patients' comfort and well-being. Up to 60-80% of patients experience anxiety before surgery. (5,6) Factors that contribute to anxiety include cultural diversity, age, gender, type of surgery and anaesthesia, previous experience with anaesthesia or surgery, and inadequate preoperative information. Studies have shown that the incidence of preoperative anxiety is higher for caesarean section and for the most common technique, regional anaesthesia (RA), than for other anaesthetic techniques and surgical procedures.. (7,8,9)

However, there are many studies in the literature about the use of hospital or suggested websites for an upcoming anaesthesia or procedure, but there is no study about the uncontrolled social media use for information and the effect on anxiety. We therefore conducted a survey of patients undergoing elective C/S at our institution to assess whether patients use social media to seek information about anaesthesia and the effect of information on their anxiety levels using the Amsterdam Anxiety Scale.

MATERIALS AND METHOD

This single-arm, prospective, observational cohort study included 250 patients scheduled for elective cesarean section at the Obstetrics and Gynaecology Department of Ankara Bilkent City Hospital. Patients were between 18 and 45 years of age, American Society of Anesthesiologists (ASA) Class I-II, who volunteered to participate in the study and were able to understand the questionnaire and give informed consent. Patients were excluded if they had major cognitive impairment or any mental disorder that could affect the results, such as inability to read and understand Turkish, and if they required emergency surgery. Patients agreed to participate by completing the study questionnaire. The sample size was set to include approximately the same number of patients as in similar studies.

This study was approved by the Ethics Review Board of Ankara Bilkent City Hospital (approval number: E1-21-1739) and registered in the Clinical Trials Registry (NCT05416541).

Each questionnaire was collected by the study coordinator. The questionnaire used for this paper consisted of three sections. (A: patient characteristics; B: internet and social media use; C: Amsterdam Preoperative Anxiety and Information Scale).

The first part analysed demographic information such as age, education, number of pregnancies, whether she had had surgery before, if so, what type of anaesthesia was used, how many caesarean sections she had, if she had had a caesarean section before, what type of anaesthesia was used.

The second part analyses internet use. It will be found out whether the patient uses the internet, if so, how often she uses it, which portals she uses most to exchange information (YouTube, Facebook, Twitter, Instagram, blogs and Google) and whether she used the internet to get information (text, video) about her anaesthesia during her pregnancy. If she has exchanged information, we will ask her opinion about the written or visual information she has seen or read. We will then ask whether she would change her choice of anaesthesia as a result of the information she found on the internet.

In the final section of the questionnaire, preoperative anxiety was assessed using the Amsterdam Preoperative Anxiety and Information Scale (APAIS), which has been translated and validated in Turkish. (10)

The APAIS is a self-report questionnaire consisting of six items. Two items assess anxiety related to anaesthesia, two items assess anxiety related to surgery, and two items assess desire for information. Thus, the APAIS assesses patients' anxiety about anaesthesia, surgery, and lack of knowledge, and the score ranges from 6 to 30. (11)

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 program (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and median (min-max), and categorical variables were expressed as number (percentage). Conformity to normal distribution was tested using Kolmogorov–Smirnov test. Student's t-test was used for comparing normally distributed data, Mann–Whitney U test was used for comparing non-normally distributed data, and Pearson's chi-square or Fisher's test was used for comparing categorical variables. $p< 0.05$ was considered statistically significant for all tests.

RESULTS

Of the 250 patients who were asked, 99.6% (n = 249) agreed to take part in the study, and the mean age was 29,22□4,59 years. The median and minimum-maximum number of parites was 2 (1-7). 82.7% (n = 206) of the patients had experience of anaesthesia.

98.8% of the patients (n=246) were internet users and 93.6% of them (n=231) were daily internet users. 68.2% (n=170) of patients had completed primary or secondary school, and the remaining 31.8% (n=79) had completed university. Internet use didn't show any correlation with education. (Table 1)

Who agreed the questionnaire (mean) (%)	99.6 (n= 249)
Age (mean)	29,22 ± 4,59 years
Parite (mean)	2
Experienced anaesthesia before (%)	82.7 (n = 206)
Education (%)	
Primary – secondary	68.2 (n=170)
University	31.8 (n=79)
Internet users (%)	98.8 (n=246)
Daily internet users (%)	93.6 (n= 231)
Read articles about C/S anaesthesia. from internet (%)	34.6 (n=85)
Watched videos about C/S anaesthesia from internet (%)	29.3 (n=72)

Among internet users, 34.6% (n=85) had read articles and 29.3% (n=72) had watched videos about caesarean section anaesthesia on the internet. The proportion of those who read articles or watched videos about caesarean section anaesthesia on the Internet was statistically significantly higher among university graduates (p<0.05). 72.9% (n=62) of those who read articles and 58.3% (n=42) of those who watched videos stated that they did not want general anaesthesia for caesarean section. 80.1% of those who had not read about caesarean section anaesthesia on the internet or 74.1% of those who had not watched a video had no opinion about anaesthesia.

APAIS anxiety scores of those who read articles about caesarean section anaesthesia on the internet were statistically significantly higher than those who did not (18 vs 15) (p=0.01). Anxiety scores of those who watched videos were statistically significantly higher (20.5 vs 15) (p=0.0001). From the answers given to APAIS scores, it was observed that anaesthesia-related anxiety was significantly higher than surgery-related anxiety (p<0.05). It was also observed that APAIS score was significantly higher in university graduates than non-university graduates (p<0.05).

DISCUSSION

The number of so-called "e-patients", patients who routinely use the Internet to obtain information about their health care, is steadily increasing. (12) In our study, we found that 98.8% of patients were internet users, and 72.9% of those who read articles and 58.3% of those who watched videos stated that they did not want general anaesthesia for caesarean section. The APAIS anxiety scores of those who read articles and watched videos about caesarean section anaesthesia on the internet were higher, and it was also observed that anaesthesia-related anxiety was significantly higher than surgery-related anxiety. This is the first study in the literature to evaluate the effect of social media on anxiety.

The participation rate was high at over 99.6%. The main finding of the survey was that most young patients had used social media and 98.8% of them used it to find out more about anaesthesia.

The motivation of these e-patients is to find the information they want quickly and easily. As only a few minutes are dedicated to the explanation of anaesthesia, this may not be enough for patients (its advantages and disadvantages, as well as risks and alternatives, if they exist). (13)

In the literature, Murero et al. showed that patients after cardiac surgery showed that one fifth of the surveyed 80 patients, Kurup et al. showed that about 40% of their 877 enrolled patients and Weiser et al. showed that less than one third of the 815 patients had used the Internet preoperatively to obtain medical information about surgical procedures not for upcoming anaesthesia. (14,15,16) In these studies, searches for elective anaesthesia are significantly lower than in our study. This is consistent with a previous report that showed that patients were significantly more afraid of surgery than of anaesthesia in the pre-anaesthesia visit. (17) From the responses to the APAIS scores in our study, anaesthesia-related anxiety was significantly higher than surgery-related anxiety. The reason for the difference from the other studies may be that the mean age was higher than in our study and the time per patient in the preoperative anaesthetic visit was longer. Again, while in these studies anaesthesia anxiety decreased with education, in our study the opposite was found.

In our study, we found that almost all of our patients used the internet and social media. Because the so-called "e-patient" seems to be younger and our mean age was 29,22 4,59 years younger than these studies and also our study group consists only of women. (3)

Various studies have reported that 73.3% to 86% of women undergoing caesarean section experience preoperative anxiety. (18) Anxiety before caesarean delivery is associated with increased incidence of hypotension after spinal anaesthesia, refusal of caesarean delivery or regional anaesthesia, also decreased Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score, readmission or prolonged hospital stay, infection, increased postoperative pain scores, increased analgesic requirement and cost of hospitals, which reduces overall maternal satisfaction with perioperative hospital services. (9,19,20) In our study, we found that 72.9% of those who read articles and 58.3% of those who watched videos from social media said they did not want general anaesthesia for caesarean section.

Therefore, identifying and reducing perioperative anxiety in women undergoing CS has become more important. The ASA reports the need for a preoperative anaesthetic assessment for all patients. The provision of anaesthesia information and preoperative educational interventions has been shown to reduce preoperative anxiety. (6) The ideal method of providing this information is unknown. Most information aimed at reducing preoperative anxiety is given to the patient verbally or in writing, but this is not always easy for the patient to understand. Recent research has shown that even when information is given to healthy, educated young volunteers in an ideal environment, recall is low. (21) Pre-operative anaesthetic counselling, hospital or procedure websites recommended by doctors are important for pre-operative anxiety levels. Because it is easy to use and accessible, women use internet social media (blogs, YouTube, Instagram, Twitter and Facebook) to reduce their anxiety. They search for information about pregnancy and parenting, share information of their choice with others, and build social networks to strengthen social support. (22)

In January 2022, there were 69.95 million internet users in Turkey. And 50.6% are women; over 40.7% are aged 18-44. The number of internet users in Turkey increased by 3.9 million (+5.9%) between 2021 and 2022, but the issues surrounding COVID-19 continue to affect research into internet penetrati-

on, so the actual number of internet users may be higher than these published figures suggest. (23) (https://datareportal.com/reports/digital-2022-turkey) Given the high level of internet use, concerns have been raised about the possibility of public manipulation by pharmaceutical marketing strategies and misleading public opinion by false claims from unreliable sources, and these should be acknowledged. (24) Other disadvantages of using social media for health information were misinformation faced by consumers and increased knowledge about the procedure, awareness of complications. (25) Similar to our study, Tanis et al. reported that unsupervised online videos can occasionally cause anxiety. (26)

CONCLUSION

It seems that we need to consider directing our patients to reliable and credible resources when appropriate. The quality of online anaesthesia information is variable, with reports of good quality information on several anaesthesia-related topics, but also that most anaesthesia information available on the World Wide Web is of poor quality, and that it is difficult for patients searching the Internet to find and understand how to evaluate good quality anaesthesia-related sites.

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Konjenital Diyafragma Hernisi Tanılı Fetüslerde Prognostik Marker Olarak Mide Pozisyonu

Stomach Position as a Prognostic Marker in Fetuses with Congenital Diaphragmatic Hernia

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ÖZ

Amaç: Konjenital diafragma hernisinde (KDH) mide pozisyonu ile neonatal sağkalım arasındaki ilişkiyi incelemek

Metod: Aralık 2019- Aralık 2022 tarihleri arasında Ankara Şehir Hastanesi Perinatoloji kliniğine başvuran 18-45 yaş ve 22-39 gebelik haftaları arasında, fetal KDH tanılı toplam 36 gebe retrospektif olarak analiz edildi. Gebelikler yenidoğan sağkalımına göre iki gruba ayrıldı. Sağkalan (n=8) ve canlı doğup ölen (n=22) gruplar arasında demografik özellikler, klinik özellikler ve kontralateral akciğer boyutu / baş çevresi (LHR) oranı, mide pozisyonu ve diğer prognostik faktörler karşılaştırıldı.

Bulgular: Ortalama anne yaşı 29,30 ± 1,02 (17-40 aralığında) olup, hastaların %36'nin (13/36) ilk gebeliğiydi. Tanı anındaki median gebelik haftası 25,10 (13.5-37,6) idi. Parite, tanı anındaki medyan gebelik haftası, KDH tipi, karaciğer pozisyonu, median LHR açısından sağkalan ve doğum sonrası kaybedilen gruplar arasında istatistiksel olarak anlamlı fark bulunmadı. Grade 2 mide pozisyonu sağkalan grupta istatiksel olarak anlamlı olacak şekilde daha yüksek saptandı (p=0,01). neonatal operasyon oranı ve 1.-5. dakika apgar skorları doğum sonrası kaybedilen gruba göre daha yüksek saptandı (p=0,02, p=0,01, p=0,00 sırasıyla).

Sonuç: KDH'de mide pozisyonu derecelendirmesi, neonatal sağkalım ile ilişkili olabilecek, pratik ve uygulanabilir bir yöntemdir ve grade 2 mide pozisyonu, LHR'den bağımsız olarak KDH'li fetüslerde artmış sağkalım ile ilişkili bir belirteç olabilir. Bu yöntem, neonatal prognozun değerlendirilmesinde ve fetal müdahalelerin mevcut olduğu üçüncü basamak merkeze maternal transfer gibi perinatal yönetimin planlanmasında yararlı olabilir.

Anahtar Kelimeler: Konjenital diafragma hernisi, mide, prognoz

ABSTRACT

Objective: To examine the relationship between stomach position and neonatal survival in congenital diaphragmatic hernia (CDH).

Study Design: A total of 36 pregnant women with a diagnosis of fetal CDH, aged between 18-45 years and 22-39 weeks of gestation, who applied Ankara City Hospital Perinatology clinic between December 2019 and December 2022, were analyzed retrospectively. Pregnancies were classified into two categories based on neonatal survival. Demographic characteristics, clinical features and contralateral lung size/head circumference (LHR) ratio, stomach position, and other prognostic indicators were evaluated among the survivor (n=8) and non-survivor (n=22) groups.

Results: The mean maternal age was 29.30 ± 1.02 (range 17-40), and 36% (13/36) of the patients were primigravid. The median gestational week at diagnosis was 25.10 (13.5-37.6). There was no statistically significant difference between the survivor and non-survivor groups in terms of CDH type, liver position, gestational week at diagnosis, and median LHR. Grade 2 stomach position was found to be statistically significantly higher in the survivor group (p=0.01). Operation rate and 1st-5th minute Apgar scores were higher than in the non-survivor group (p=0.02, p=0.01, and p=0.00, respectively).

Conclusion: Stomach position grading in CDH is a practical and applicable method associated with neonatal survival, and grade 2 stomach position may be a marker associated with increased survival in fetuses with CDH regardless of LHR. It may be useful in assessing neonatal prognosis and planning perinatal management, such as maternal transfer to a tertiary center where fetal interventions are available.

Keywords : Congenital diaphragmatic hernia, prognosis, stomach

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a developmental disorder of the diaphragm that results in herniation of the abdominal organs into the fetal thorax. CDH is a relatively common anomaly with an incidence of 1 in 2500 live births (1). While in the postpartum period, the diaphragmatic defect can be repaired surgically, pulmonary hypoplasia caused by CDH and pulmonary hypertension can increase morbidity and mortality in the neonatal period (2). Postpartum mortality rates can range from 15% to 50% in isolated cases (3, 4).

Several prenatal variables influence the survival of newborns with CDH (5, 6). Numerous prognostic factors are used for survival prediction, clinical decision-making, and counseling (7). The most commonly used parameters are the ratio expressed as the ratio of the contralateral lung area to the fetal head circumference (LHR), obtained in a cross-section of the fetal thorax, and the determination of the intrathoracic liver position. Fetal LHR is used to indirectly measure lung volume in postnatal prognosis. Patients with right-sided CDH, chromosomal abnormalities, severe congenital anomalies, liver herniation, hydrops fetalis, and low fetal LHR have a poor prognosis. (6, 8).

More recent studies have begun investigating the predictive role of stomach position on neonatal survival in CDH, and various grading systems have been developed (9, 10). A study by Cordier et al. found that prenatal stomach position grades could potentially predict neonatal survival, the need for neonatal mesh repair, the need for extracorporeal membrane oxygenation (ECMO), and the need for long-term respiratory support (9). However, there is a paucity of data in the literature on this topic, for which there needs to be more studies.

The aim of our study is to investigate the relationship between fetal stomach position and neonatal survival in pregnancies with CDH and to evaluate obstetric outcomes.

MATERIALS AND METHOD

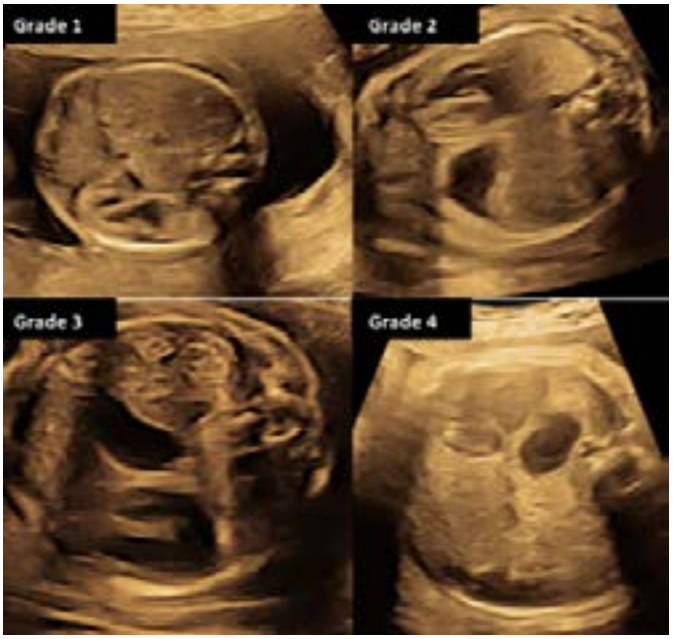
A total of 36 pregnant women diagnosed with fetal CDH who presented to the perinatology clinic of Ankara City Hospital between December 2019 and December 2022 were retrospectively analyzed. The study protocol was approved by the Ethics Committee of Ankara City Hospital (Decision No: E2-23-3737). The general principles of the Declaration of Helsinki were followed, and informed consent was obtained from all patients.

A total of 36 pregnant women between the ages of 18 and 45 years who were diagnosed with CDH and were between 22 and 39 weeks pregnant were included in the study. Cases with premature rupture of membranes and multiple pregnancies were excluded from the study. Cases were evaluated for demographic and clinical characteristics, ultrasound findings, and obstetric and neonatal outcomes. Pregnancy termination rate, invasive prenatal diagnostic tests, chromosomal abnormalities, and concomitant congenital anomalies were recorded. According to neonatal survival, patients were divided into two groups. Maternal age, gravida, parity, median week of gestation at diagnosis, CDH type, fetal stomach position, presence of liver and intestinal herniation, LHR, median week of gestation at delivery, birth weight, 1-5. Minute Apgar score, mode of delivery, and neonatal operation rate were compared. The percentages of liver and intestinal herniation, LHR, and neonatal operation rates were examined between groups according to stomach position.

Prenatal ultrasonography

A maternal-fetal medicine specialist performed all prenatal ultrasound examinations using transabdominal sonography (Voluson E8; GE Medical Systems). LHR was defined as the ratio of the product of the two longest vertical measurements of the contralateral lung area to the fetal head circumference in a four-chamber transverse section of the fetal thorax. The stomach position was graded as suggested by Cordier et al., in the four-chamber transverse section of the fetal heart used for LHR measurement (9): Grade 1: stomach cannot be visualized, grade 2: stomach is anterior, visualized at the level of the apex of the heart, there is no structure between stomach and apex, grade 3: abdominal organs are present anterior and posterior to the stomach, the stomach is mostly anterior according to the level of the atrioventricular valves, and grade 4: most of the stomach is behind the level of the atrioventricular valve (Figure 1).

Figure 1. Ultrasonography images. Prenatal stomach position. Grades 1–4, Cordier et al. According to the rating system. Grade 1: abdominal, no stomach is observed in the thorax. Grade 2: anteriorly located stomach in the thorax, Grade 3: stomach in the mid-posterior thorax. Grade 4: retrocardiac.



Statistics

The Statistical Package for the Social Sciences was used to conduct statistical analyses. (IBM SPSS Statistics for MAC, version 22.0). Visual (histograms, probability plots) and analytic methods (Shapiro-Wilk test) were used to determine whether variables were normally distributed. In descriptive analyses, the median was used for variables that were not normally distributed. The Mann-Whitney U test was used for comparison between groups when continuous variables were not normally distributed. The Kruskal-Wallis test was used to test the significance of the difference between three or more groups for non-normally distributed groups. If applicable, the chi-square and Fisher's exact tests were used to compare categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

The mean maternal age was 29.30 ± 1.02 years (range, 17-40 years), and 39% (14/36) of pregnant women were primiparous.

The median gestational week at diagnosis was 25.1 (13.5-37.6). Amniocentesis was used to analyze the fetal karyotype in 12 cases (33%), and it was reported that 9 of them had a normal karyotype. Of the three abnormal karyotypes, one fetus was found to have trisomy 12, one fetus was found to have a 15q13.3 duplication, and the other fetus was found to have Matthew Wood syndrome. Left-sided CDH was present in 28 (78%) fetuses and right-sided CDH in 5 (19%) fetuses, posterolateral hernia in 2 fetuses (6%), and posterior hernia in 1 fetus (3%). Congenital structural anomalies were found in 14 (39%) fetuses. Cardiovascular (21%) and genitourinary (6.1%) were the most common system anomalies. Intestinal herniation was present in 57.6%, and liver herniation in 42% of patients. After appropriate counseling, three families requested termination of pregnancy. In addition to CDH, one fetus had holoprosencephaly, one had a clenched hand and aberrant right subclavian artery (ARSA), and the other had a neural tube defect. The median week of termination was 22 weeks.

While 3 (9%) of 33 fetuses with CDH died intrauterine, 8 (24%) of 30 live births survived after birth. No significant difference was found between the survivor group (n=8) and the non-survivor group (n=22) in maternal age, week of diagnosis, type of CDH, LHR values, week of birth, and birth weight ($p > 0.05$) (Table 1).

Table 1. Comparison of demographic obstetric and neonatal outcomes among neonatal survival groups

	Survivor (n= 8)	**Non-survivor (n= 22)**	**p-value**
Maternal age (year)	26.5 (26-36)	30 (18-42)	0.48
Gravida (n)	1.5 (1-6)	2 (1-6)	0.71
Parity (n)	0.5 (0-4)	1 (0-4)	0.71
Gestational week at the time of diagnosis	29.9 (16-37)	24.7 (13-37)	0.32
CDH type			0.30
Left	8 (100%)	18 (81%)	
Right	0 (0%)	2 (9%)	
Posterolateral	0 (0%)	1 (5%)	
Posterior	0 (0%)	1 (5%)	
Intestinal herniation			0.70
present	7 (88%)	15 (6%8)	
none	1(12%)	7 (32%)	
Liver position			0.05
Thorax	2 (25%)	14 (64%)	
Abdomen	6 (75%)	8 (6%)	
Additional anomaly			0.20
Izole	6 (75%)	11 (50%)	
Non-izole	2 (25%)	11 (50%)	
LHR	1.7 (0.8-2.8)	0.8 (0.2-2.3)	0.07
Week of birth	37.9 (36-39)	38.4 (25-39)	0.60
Birth weight	3065 (2800-3440)	2640 (770-3790)	0.08
Mode of delivery			0.18
Vaginal delivery	1 (12.5%)	6 (62.5%)	
Cesarean section	7 (87.5%)	16 (37.5%)	
1.min apgar score	5 (4-8)	2 (0-6)	0.01
5.min apgar score	7.5 (6-9)	4 (0-8)	0.00
Neonatal operation			0.02
present	8 (100%)	4 (18%)	
none	0 (0%)	18 (81%)	

CDH, congenital diaphragmatic hernia; LHR, lung-to-head ratio

Values were presented as median (min-max), number, percentile (n, %)

$p < 0.05$ was considered statistically significant

It was found that 100% of the surviving neonates underwent surgery in the neonatal period, and it was observed that Apgar scores were higher in the first to fifth minutes (p=0.01 and p=0.00, respectively). The rate of herniation of the liver and intestines into the thorax was similar in the survival groups. When compared by stomach position, grade 2 stomach position was statistically significantly higher between survival groups (p=0.01) (Table 2).

Table 2. Comparison of stomach position degrees among neonatal survival groups

	Survivor (n=8)	Non-survivor (n=22)	p-value
Stomach position			
Grade 1	2 (25%)	10 (55%)	0.38
Grade 2	4 (50%)	1 (5%)	0.01
Grade 3	1 (12.5%)	7 (32%)	0.23
Grade 4	1 (12.5%)	4 (18%)	0.77

Values were presented as number, percentile (n, %)

p < 0.05 was considered statistically significant

Chi-square test

While neonatal surgery rates were higher for grade 2 stomach position, LHR and liver and intestinal herniation rates were similar (Table 3).

Table 3. Comparison of the clinical and ultrasonographic features of the groups formed according to the degrees of stomach position

	Stomach position				
	Grade 1 (n=12)	Grade 2 (n=6)	Grade 3 (n=9)	Grade 4 (n=6)	p-value
LHR	1.7 (0.2- 2.8)	1.8 (0.5-2.8)	1.3 (0.7-6.6)	0.7 (0.3-3.1)	0.13
Liver herniation	5 (45%)	3 (50%)	4 (57%)	4 (80%)	0.60
Intestinal herniation	7 (70%)	5 (100%)	5 (71%)	3 (100%)	0.21
Neonatal operation	3 (25%)	6 (50%)	2 (17%)	1 (8%)	0.03
Izole CDH	7 (58%)	4 (66%)	4 (44%)	4 (68%)	0.79

CDH, congenital diaphragmatic hernia; LHR, lung-to-head ratio

Values were presented as median (min-max), number, percentile (n, %)

p < 0.05 was considered statistically significant

Kruskal-Wallis test, chi-square test

DISCUSSION

In our study, stomach position ratios were examined among the survival groups were investigated. Whereas the LHR ratio was similar, Grade 2 stomach position was found to be higher in neonates who survived postnatally. These results suggest that prenatal grade 2 stomach position may be a marker associated with increased survival in CDH independent of LHR.

Advances in prenatal diagnosis and the discovery of predictive factors in CDH have led to improved fetal and neonatal management in appropriate tertiary centers. There are limitations in measuring LHR, the most commonly used parameter, such as variations among physicians performing ultrasound and difficulties in determining the border of the hypoplastic lung in severe forms of CDH (7, 11). In addition, uncorrected LHR has been demonstrated to increase with gestational age (12-14). For this reason, studies on using organs herniated into the thorax as direct and indirect markers have come to the forefront. There are publications in which the location and volume of the stomach and liver in CDH have been studied by MRI (9, 15).

In recent years, prenatal stomach position has been recommended for predicting neonatal prognosis (16-18). Some publications in the literature use different methods to evaluate fetal stomach position in pregnancies with CDH. A study by Kitano et al. described a 4-level grading system for stomach position; the classification was made according to the rate of stomach herniated to the thorax (10). Cordier et al., on the other hand, classified the stomach according to its position in the thorax relative to the atrioventricular valve plane and studied the correlation between the liver position detected on MRI and the stomach position grades (9). They showed that grading stomach position on prenatal ultrasound is a very reliable and simple method for indirectly assessing liver herniation to thorax in left-sided CDH. Using the stomach position grading method by Cordier et

al., our study found that grade 2 stomach position was associated with long-term neonatal survival. The fact that the LHR ratio was statistically similar among the survivor and non-survivor groups also suggests that this method may be a practical and reproducible predictor independent of LHR.

Tanacan et al. similarly classified the location of the stomach in their study of 44 pregnant women with CDH. They found that the stomach was in the abdomen in more than 50% of the surviving neonates, second most commonly in the anterior left thorax (19). Our study found a grade 2 stomach position in 50% of the surviving infants, suggesting an increased survival rate. Another recent study compared groups with similar LHR ratios in infants with left-sided CDH without liver herniation and found that neonatal morbidity was lower in infants with stomach in the abdomen than in infants with gastric hernia (20).

Prenatal estimation of neonatal respiratory morbidity in CDH is not entirely possible because the lungs are not functional until after birth. Both the degree of stomach position and LHR can be considered indicators of pulmonary hypoplasia, reflecting the likelihood of survival and the degree of respiratory morbidity. The study performed by Weller et al. showed that the time to resolution of pulmonary hypertension on echocardiography increased with increasing degree of prenatal stomach position(15). The increased neonatal survival seen in our study may be related to decreased respiratory morbidity. Studies in the literature indicate a linear correlation between the need for ECMO and the degree of stomach position(17). The advantages of our study are that the cases had homogen obstetric characteristics, and the same physician investigated the stomach position using prenatal ultrasound data. Limitations are the retrospective design and the criteria for long-term survival in assessing neonatal prognosis, and morbidities such as pulmonary hypertension and chronic lung disease that develop in the postnatal period were not included in the analysis. Therefore, further studies are needed for definitive conclusions.

CONCLUSION

Stomach position grading in CDH is a practical and applicable method associated with neonatal survival, and grade 2 stomach position may be a marker associated with increased survival in fetuses with CDH regardless of LHR. It may be useful in assessing neonatal prognosis and planning perinatal management, such as maternal transfer to a tertiary center where facilities such as fetal interventions are available.

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Özgün Araştırma Original Article

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Evaluation of Fetal Thymus in Pregnancies with Inflammatory Bowel Disease

İnflamatuar Bağırsak Hastalığı Tanılı Gebelerde Fetal Timusun Değerlendirilmesi

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ÖZ

Amaç: İnflamatuar barsak hastalığı (İBH) ile komplike olmuş gebeliklerde fetal timik-torasik oranı araştırmaktır.

Metod: Bu vaka-kontrol çalışmasına 28-40. gebelik haftalarında bulunan Ülseratif Kolit (ÜK) ve Crohn Hastalığı (CH) tanılı 26 hasta ile 26 sağlıklı gebe dahil edildi. Kontrol grubu, gebelik yaşı ile eşleşen komplikasyonsuz gebeliklerden seçildi. Ultrasonografik değerlendirme sonrasında demografik özellikler, hastalık tipi ve hastalık aktivitesi değerlendirildi. Timik-torasik oran (TTO), ön-arka timus ölçümünün intratorasik mediastinal çapa bölünmesiyle hesaplandı.

Bulgular: TTO ölçümleri vaka grubunda 0,32±0,02 ve kontrol grubunda 0,35±0,02 idi (p <.001). Vaka grubundaki hastaların %34,6'sı (n=9) gebelikleri boyunca en az bir kez atak geçirmişti. ÜK ve CH olan hasta grupları arasında medyan TTO değerleri açısından anlamlı fark yoktu. Gebelikte en az bir kez atak geçiren grupta TTO, atak geçirmeyenlere göre anlamlı olarak daha düşük bulundu (sırasıyla 0,31'e karşılık 0,34, p=.012).

Sonuç: Çalışmamız İBH'nın fetal TTO üzerindeki etkisini değerlendiren ilk çalışmadır. İBH'li gebelerde maternal akut ve kronik inflamasyon, intrauterin çevreyi değiştirerek fetal timus boyutunu etkileyebilir. Gebelikte geçirilen atakların fetal timus boyutunu etkileyebileceği düşünüldüğünde bu hastaların remisyonda tutulması ve yakından takip edilmesi çok önemlidir.

Anahtar Kelimeler: İnflamatuar barsak hastalığı, Ülseratif Kolit, Crohn hastalığı, Fetal timus, Timik-torasik oran

ABSTRACT

Objective: To investigate the fetal thymic-thoracic ratio in pregnancies complicated with inflammatory bowel disease(IBD)

Study Design: This case-control study included 26 pregnant women diagnosed with Ulcerative Colitis (UC) and Crohn's Disease (CD) and 26 healthy pregnant women at 28-40 gestational weeks. The control group was selected from uncomplicated pregnancies matched by gestational age. Demographic characteristics, disease type, and disease activity were assessed after ultrasonographic evaluation. The thymic-thoracic ratio (TTR) was calculated by dividing the anteroposterior thymus measurement by the intrathoracic mediastinal diameter.

Results: TTR measurements were 0.32±0.02 in the case group and 0.35±0.02 in the control group (p <.001). 34.6% (n=9) of the patients in the case group had an attack at least once during pregnancy. There were no significant differences in the median TTR values between UC and CD groups. TTR was significantly decreased in the group who had an attack at least once during pregnancy compared to those who did not (0,31 vs. 0,34, respectively, p=.012).

Conclusion: This is the first study to assess the impact of IBD on fetal TTR. Maternal acute and chronic inflammation in pregnancies with IBD may affect the fetal thymus size due to the intrauterine milieu. Considering that exacerbation during pregnancy also affects fetal thymus size, it is crucial to keep these patients in remission throughout the disease and follow up closely.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, Fetal thymus, Thymic-thoracic ratio

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are categorized as inflammatory bowel diseases (IBD), which cause digestive disorders and inflammation in the gastrointestinal tract (1). Both diseases are often diagnosed in childbearing and mainly affect women of reproductive age. Although the etiopathogenesis of IBD is not yet fully understood, studies on this subject emphasize the role of genetic, environmental factors, and gut microbiota (2, 3). The interaction between these factors contributes to the inappropriate immune response. Stimulation of the immune system causes damage to the gastrointestinal tract and symptoms in different parts. While CD has a segmental, asymmetric, and transmural manner in the digestive tract, UC is generally characterized by mucosal inflammation that begins in the rectum and can expand to the proximal colonic segments (4).

Recent studies indicate that cytokines have a crucial role in controlling intestinal inflammation and its clinical symptoms associated with IBD, thus directly involved in the pathogenesis of IBD (5). Environmental triggers lead to excessive and aberrant cytokine response in the genetically sensitive host, thus resulting in subclinical or acute inflammation. The defective acute inflammatory response results in inadequate clearance of antigenic factors; therefore, mucosal immune cells such as macrophages and T cells respond by producing cytokines, ultimately establishing chronic gastrointestinal tract inflammation (6). The disproportion between pro-inflammatory and anti-inflammatory cytokines restricts the resolution of inflammation and leads to disease progression and tissue destruction. In addition to continuing inflammation, attempts to resolve inflammation by angiogenesis and induced remodeling by the immune system lead to the ongoing process of the disease with remissions and attacks. Women with disease exacerbation at conception have more potential to have an attack during pregnancy than those who become pregnant while in remission (7). So, patients with active disease had an increased risk of adverse pregnancy outcomes such as spontaneous abortion, small for gestational age, low birth weight, and preterm birth due to impaired nutritional uptake and absorption (8).

The fetal thymus is essentially an epithelial organ that provides an appropriate environment for developing T-lymphocytes. These T-lymphocytes mature over time and are called thymocytes, enabling the thymus to play a crucial role in systemic inflammatory processes(9). Chaoui et al. first described the anteroposterior fetal thymus and the intrathoracic mediastinal diameter in the three vessels' view to complete the thymic-thoracic ratio(10). Reference charts for thymus measurement have been developed, and it has been shown that fetal thymus size is not affected by gender and multiple pregnancies (11, 12). Previous studies have shown an association between fetal thymus measure and several maternal or fetal disorders. Small thymus measurements in fetuses diagnosed with congenital heart disease and 22q11 microdeletion, Down syndrome, and intrauterine growth retardation are some examples of fetal conditions (10, 11, 13). Small thymus size has been detected in pregnancy complications such as gestational diabetes mellitus, preeclampsia, and premature rupture of membranes (14-16). In addition, our previous studies showed decreased fetal thymic-thoracic ratio in various rheumatological diseases (17, 18). So, we aimed to obtain the fetal thymic-thoracic ratio in the pregnancies with IBD compared to a healthy control group.

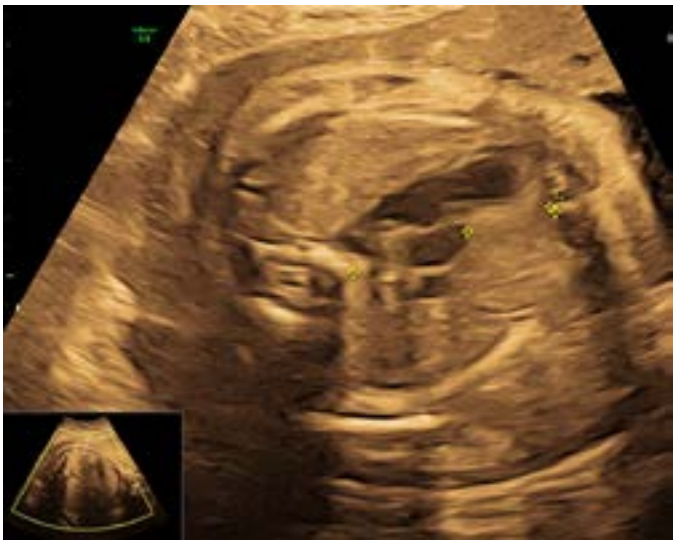
MATERIALS AND METHOD

We performed a case-control study on 52 pregnant women from 28 to 40 weeks gestation. All patients in our study were collected in the perinatology clinic of Ankara City Hospital in Turkey from July 2022 to January 2023. After approval from the Medical Research Ethics Department of Ankara City Hospital, this study was planned following the Declaration of Helsinki (E2-22-2142). All participants wrote the informed consent.

Pregnant women diagnosed with UC and CD before pregnancy and followed up in our clinic were included. Other chronic diseases, smoking, multiple pregnancies, pre-eclampsia, pregnancies with congenital structural or chromosomal abnormalities, and intrauterine growth restriction were excluded to minimize confounding effects. A blinded maternal fetal subspecialist (D.M.B.) performed all sonographic measurements using the 4-8 MHz convex transducer of Voluson E8 (G.E. Healthcare, Milwaukee, WI). Demographic characteristics, including age, gravidity, parity, abortus, pre-pregnancy body mass index (BMI), disease type, and disease activity, were assessed after ultrasonographic evaluation. The gestational week of all study groups was defined according to the last menstrual period or based on the measurement of first-trimester crown-rump length. An increased frequency in symptoms and at least one attack was set as having an attack during pregnancy. For the control group, healthy pregnant women matched by maternal age and gestational weeks were chosen randomly. None of our patients were treated with betamethasone administration before the sonographic evaluation.

Firstly, the homogeneous construction of the thymus was visualized in the anterior part of the mediastinum. In the three-vessel view, the distance between the posterior wall of the fetal chest and the transverse aortic arch edge was calculated to evaluate the anteroposterior diameter, as previously described (10). The intrathoracic mediastinal diameter was the distance of a parallel section drawn from the anterior border of the thoracic vertebral body along the epicenter of the aortic arch vessel to the inner edge of the sternum also measured. The thymic-thoracic ratio (TTR) was estimated by dividing the anteroposterior thymus by the intrathoracic mediastinal diameter (Figure 1).

Figure 1: The anteroposterior diameter of the fetal thymus (1) and the intrathoracic mediastinal diameter (2)



Measurements were repeated, and the average values of three measures were recorded.

All statistical analyses were performed using the Statistical Package for Social Sciences software version 17.0 (SPSS Inc, Chicago, IL). Normal distributed continuous variables are reported as mean ± standard deviation. Nonnormally distributed metric variables are presented as median (Inter Quartile Ranges). Demographic features of the study groups were compared using the Independent t-test and Mann-Whitney U test. The differences in TTR values between the case and control groups were evaluated using the Independent t-test. Mann-Whitney U test was also used in the comparisons made according to the type of disease and the presence of attacks. P-values≤0.05 were assessed as statistically noticeable.

RESULTS

This study included the case group comprising 26 patients, 15 UC and 11 CD, and the control group composed of 26 patients. Clinical characteristics of the study groups and fetal TTR measurements between case and control groups were presented in Table 1.

Table 1: Demographic and clinical characteristics of all participants

	Case group (n=26)	**Control group (n=26)**	**p-value**
Age (years)	28.5±5.6	29.8±4.5	.327*
Gravidity	3±2	3±2	.297†
Parity	1 (0-1)	1 (0-2)	.711†
Abortus	0 (0-1)	0 (0-0)	.063†
Pre-pregnancy BMI (kg/m²)	24.2±1	25.2±2.3	.079*
Gestational age (Weeks)	31 (29-33)	30 (28-33)	.901†
TTR	0.32±0.02	0.35±0.02	**<.001***
Attacks during pregnancy	9 (34.6%)		
Gestational age at birth (weeks)	38 (36-39)	38 (37-40)	.063†
Birth weight (gram)	2780 (2540-3010)	3240 (3010-3510)	**.031†**
Apgar 1st score	7 (6-8)	7 (7-8)	.412†
Apgar 5th score	9 (8-10)	9 (8-10)	.841†

Values are presented as mean± standard deviation and median (IQR (Inter Quartile Ranges)) or as counts (percentage)

The bold characters were used to define the significant "p" values p < 0.05.
Abbreviations: TTR; thymic-thoracic ratio

* Independent t-test

† Mann Whitney U test

Both groups had similarities in pre-pregnancy body mass index, age, gravidity, and abortion numbers. TTR values were 0.32±0.02 in the case group and 0.35±0.02 in the control group (p <.001). The birth outcomes of both groups were also compared. There was only one fetus in the case group who were admitted to the neonatal intensive care unit. 34.6% (n=9) of the patients in the case group had an attack at least once during pregnancy.

Table 2: Comparison of the thymic-thoracic ratios between subgroups

	UC (n=15)	**CD (n=11)**	**p-value**	**Attacks during pregnancy (n=9)**	**No Attacks during pregnancy (n=17)**	**p-value**
TTR	0.32 (0.31-0.34)	0.32 (0.31-0.36)	.813†	0.31 (0.31-0.32)	0.34 (0.32-0.36)	**.012†**

Values are presented as median (IQR (Inter Quartile Ranges))

The bold characters were used to define the significant "p" values p < 0.05.
Abbreviations: UC; Ulcerative colitis , CD; Crohn's disease , TTR; thymic-thoracic ratio

† Mann Whitney U test

Table 2 shows the comparison of TTR values in IBD subgroups. No significant difference in the median TTR values was observed between UC and CD groups. TTR was statistically significantly decreased in the group who had an attack at least once during pregnancy compared to those who did not (0,31 vs. 0,34, respectively, p=.012).

DISCUSSION

This study showed decreased fetal TTR in pregnant women with IBD. Although we found no difference between UC and CD groups, TTR was smaller in these patients than in controls. We also showed that pregnant women with at least one attack had a smaller TTR than those without during pregnancy.

During fetal development, various organs and systems are formed and matured. These processes can be disrupted and made vulnerable to inflammation. Inflammation may be caused by various factors during pregnancy, including infections, immune system dysregulation, or exposure to certain environmental factors (9). It is crucial to understand the impact of inflammation on the developing fetus, as it can significantly affect the development of various fetal organs. The thymus is a primary lymphoid organ susceptible to inflammation, stress, hormonal status, and the inadequacy of nutrition. The dynamics in the immune system and inflammatory processes trigger the fetal hypothalamic-pituitary-adrenal axis, resulting in the thymus's cellular density and composition (19). With the induction of apoptosis, changes begin with the reduction of cortical lymphocytes, followed by the disappearance of the corticomedullary demarcation line and atrophy in organ size. Therefore, the fetal thymus has been an essential source of research used to evaluate the effect of maternal inflammatory and oxidative conditions on the fetus. Hyperglycemia and metabolic disturbance caused by diabetes are stress factors for the fetus and decreased fetal thymus size has been observed in these patients (20). Glucose excess and metabolic disturbance seen in maternal diabetes cause a fetal stress cycle due to impaired oxygen transfer of the placenta. The reduced fetal thymus size observed in maternal diabetes has been associated with this vicious circle. The activated hypothalamic-pituitary axis and increased maternal cortisol transfer in preeclampsia have been associated with fetal thymus involution and decreased fetal thymus size in these patients (14). Small fetal thymus dimension is also demonstrated in various other stress-associated conditions in pregnancy, including fetal inflammatory response syndrome, chorioamnionitis, and malnutrition (21-23). However, in the absence of noticeable infection, thymocyte depletion and thymus involution in chorioamnionitis have been shown histologically. The decreased fetal thymus size observed after the COVID-19 infection also indicates that maternal inflammatory mediators may be able to trigger the processes affecting fetal thymus involution (24). In light of this information, it was thought that the fetus might undergo modifications in some organs in response to infection-induced stress factors, and changes in the fetal thymus structure, which is an organ sensitive to fetal stress, may play a role in this response.

Chronic inflammation, affected by the intrauterine environment, has been observed to impact fetal thymus size (25). Epigenetic changes leading to various diseases have been observed in the innate immune cells of fetuses exposed to in-utero maternal inflammation (26). Active inflammatory processes in women with IBD may interrupt appropriate placentation or restrict the placenta's ability to meet fetal needs, thus leading to the alteration of cellular components at the maternal-fetal interface (8). Increased levels of chemokines and cytokines in IBD may lead to changes in fetal immune response. Decreased fetal thymus size in IBD revealed in our study indicated the fetal response to inflammation. This finding was consistent with our previous study, which showed reduced fetal thymus in maternal autoimmune diseases (17). Contrary to this, a previous study found increased fetal thymus size in rheumatologic diseases (27). We think the retrospective design of this previous study may have influenced the results.

Abnormal and excessive cytokine formation in IBD causes a subclinical or acute reaction. In patients who fail to resolve acute bowel inflammation, chronic inflammation develops. The imbalance between proinflammatory and anti-inflammatory inhibits the resolution of inflammation and leads to disease exacerbation and tissue destruction (6). A recent meta-analysis indicated that IBD flares during the periconceptional period and pregnancy are related to an increased risk of adverse pregnancy outcomes such as spontaneous abortion, preterm birth, and low birth weight (28). The decreased fetal thymus size in those who had an attack in our study suggested the fetal effects of inflammatory load in these patients. This shows that pregnancy should be planned while the disease is in remission, and continuous disease control is essential even during pregnancy.

The strength of our study was that it was a prospective case-control design. The limitations of our study are that fetal thymus measurement was only given as thymus-thorax ratio, serum inflammation markers were not available, its relatively small number of patients, and postnatal thymic evaluation could not be performed.

CONCLUSION

To date, this is the first study to assess the influence of IBD on the fetal thymic-thoracic ratio. Maternal acute and chronic inflammation in pregnancies with IBD may affect the fetal thymus size due to the intrauterine milieu. Considering that exacerbation during pregnancy also affects fetal thymus size, it is crucial to keep these patients in remission throughout the disease and follow up closely.

Conflicts Of Interest

The authors have no conflicts of interest.

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Özgün Araştırma / Original Article

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Mild thrombocytopenia and postpartum hemorrhage in pregnancies with placenta previa

Plasenta previa tanısı olan gebelerde hafif trombositopeni ile postpartum kanama ilişkisi

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ÖZ

Amaç: Doğum sonu kanama (PPK), maternal mortalite ve morbiditenin önemli bir nedenidir. Trombositopeni, doğum sonu kanama için bilinen risk faktörlerinden biri olmasına rağmen, hafif trombositopeninin doğum sonu kanama üzerindeki etkisi hakkında çok az şey bilinmektedir. Bu çalışma, plasenta previalı gebelerde doğum sonu kanama ile hafif trombositopeni arasındaki ilişkiyi araştırmayı amaçladı.

Metod: 1 Ekim 2019 ve 1 Mayıs 2022 tarihleri arasında plasenta previa ameliyatı geçirmiş gebelerde retrospektif bir kohort çalışması gerçekleştirdik. Çalışma grubunu hafif trombositopenisi (trombosit sayısı 100.000-149.999/ µl) olan kadınlar oluşturdu. Kontrol grubundaki kadınların trombosit sayıları normaldi (trombosit sayısı 150.000- 450.000 / µl). Sonuç, aşağıdakilerden birinin veya daha fazlasının bir kombinasyonu olan doğum sonu kanama insidansıydı: 1) intraoperatif veya doğum sonrası dönemde eritrosit süspansiyonu transfüzyonu gerekliliği; 2) Doğum öncesi döneme göre doğum sonrası hemoglobin düzeylerinde en az 3 gr/dL azalma.

Bulgular: Çalışmada 170 gebe mevcuttu; 30'u hafif trombositopenili grupta, 140'ı kontrol grubundaydı. Hafif trombositopeninin doğum sonu kanama ile ilişkili olduğu bulundu (düzeltilmiş olasılık oranı: 3.90 %95 GA: 1.56-9.72). Ayrıca hafif trombositopeni grubunda kan transfüzyonu alan ve hemoglobin düşüşü >3 g/dL olan hasta sayısı kontrol grubuna göre anlamlı olarak yüksekti (p<0,05).

Sonuç: Plasenta previa hastalarında, ameliyat öncesi hafif trombositopeni, doğum sonu kanama riskinin artmasıyla bağlantılıydı.

Anahtar Kelimeler: kan transfüzyonu, plasenta previa, plasenta akreata spektrumu, postpartum kanama, hafif trombositopeni

ABSTRACT

Objective: Postpartum hemorrhage (PPH) is a major cause of maternal mortality and morbidity. Although thrombocytopenia is one of the known risk factors for postpartum hemorrhage, little is known about the effect of mild thrombocytopenia on PPH. The current study aimed to investigate the relationship between postpartum hemorrhage and mild thrombocytopenia in pregnant women with placenta previa.

Materials and Methods: We conducted a retrospective cohort study of pregnant women who underwent placenta previa surgery between October 1, 2019 and May 1, 2022. Women with mild thrombocytopenia (platelet count 100,000-149,999/ µl) comprised the study group. The women in the control group had normal platelet counts (platelet count 150.000- 450.000 / µl). The outcome was the incidence of postpartum hemorrhage which is a combination of one or more of the following: 1) the requirement for a transfusion of pRBC during the intraoperative or postpartum period; 2) a decrease in Hb levels of at least 3 gr/dL postpartum compared to prepartum.

Results: There were 170 women in the study; 30 were in the group with mild thrombocytopenia and 140 were in the control group. Mild thrombocytopenia was found to be associated with postpartum hemorrhage (adjusted odds ratio: 3.90 95% CI: 1.56-9.72). Also in the mild thrombocytopenia group, the number of patients receiving blood transfusion and Hb decline >3 g/dL were significantly higher compared to the control group (p<0.05).

Conclusion: In placenta previa patients, preoperative mild thrombocytopenia was linked to an increased risk of postpartum hemorrhage.

Keywords: blood transfusion, mild thrombocytopenia, postpartum hemorrhage, placenta previa, the spectrum of placenta accreta

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INTRODUCTION

Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality (1). Prior to delivery, identifying the risk factors for PPH enables the team to prepare the required supplies and blood products (2). Although thrombocytopenia is one of the definite risk factors of hemorrhage, it has not been adequately studied.

Thrombocytopenia is defined as a platelet count less than 150,000/microliter (µl) (3,4). The platelet threshold, which poses a risk for postpartum bleeding, has been reported as 70-100,000 / µl in different studies (5,6). While platelet count <100.000 / µl is seen 1%, mild thrombocytopenia (defined as platelet count between 100.000-149.999 / µl) is seen 10% in pregnant women (7), and the relationship of mild thrombocytopenia with PPH remains unclear.

Recently, the relationship between mild thrombocytopenia and PPH has been studied in the uncomplicated pregnant population (7-11) and there have been studies that found its relationship with increased blood loss and blood transfusion (7,9,11). However, none of these studies investigated the relationship between mild thrombocytopenia and PPH in a group with a high risk of bleeding such as placenta previa.

Placenta previa (PP) is characterized by the abnormal placenta overlying the endocervical os. PP is often complicated by the spectrum of placenta accreta (PAS), which is caused by the invasion of the placental villi below the decidua basalis. PAS may unexpectedly cause catastrophic blood loss, multiple complications, and even maternal death (12). The incidence of PPH has increased in PP due to the inability of the uterine segment with abnormal implantation to contract as effectively as a normal uterine segment. The increased number of PAS and the risk of the cesarean incision passing through the placenta also increase PPH in PP cases (13).

The aim of the present study was to determine the relationship between mild thrombocytopenia and PPH in the pregnant women with PP.

MATERIALS AND METHOD

We performed a retrospective cohort study with pregnant women who were operated for PP in a single tertiary center between 01 October 2019 and 01 May 2022. This study was approved by Ankara City Hospital Ethics Committee (E2-22-2201). All patients included in the study underwent a cesarean delivery with the indication of PP and had platelet and hemoglobin levels within 24 hours before delivery. The study group included women with mild thrombocytopenia (platelet count 100.000-149.999/ µl). The control group included women with normal platelet count (platelet count 150.000- 450.000 / µl). Women with severe thrombocytopenia (<100.000), thrombocytosis (>450.000), multiple gestations, abruption, and coagulopathy were excluded. Cases with missing information also were excluded.

Maternal age, gestational age, gravida, parity, preoperative and postoperative hemoglobin (Hb) levels, preoperative platelet levels, patients receiving packed red blood cells transfusion (pRBC), length of stay in the intensive care unit (ICU) were obtained from patient medical files and electronic recording media. Patients who were diagnosed with PAS, underwent a hysterectomy after cesarean section (C/S), required uterine balloon tamponade and pRBC transfusion were recorded.

The outcome was the incidence of PPH, which is a combination of one or more of the following: 1) the requirement for a transfusion of pRBC during the intraoperative or postpartum period; 2) a decrease in Hb levels of at least 3 gr/dL postpartum compared to prepartum. The postpartum Hb value was used as the hemoglobin level at postoperative 24 hours. The criteria for the transfusion of pRBC are any of the following: 1) visually estimated excess intraoperative blood loss; 2) clinically severe uncontrollable ongoing hemorrhage; 3) symptomatic anemia (maternal tachycardia>100/minutes, dizziness, syncope, orthostatic hypotension) in the presence of Hb 7–8 g/dL; or (3) intraoperative or postpartum Hb level<7 g/dL regardless of symptoms (11). Due to the method's stated inaccuracy, we did not use 'clinical estimation of blood loss as an outcome measure (14).

Statistical analysis

Statistical analysis was enforced using IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median and minimum–maximum values for numerical data that do not follow a normal distribution. The normality of the variables was tested with both Shapiro–Wilk and Kolmogorov–Smirnov tests. Groups were compared with the Student t-test and Mann–Whitney U-test. A type-1 error less than 0.05 was considered statistically significant. Univariable analysis was performed to assess candidate variables as risk factors for PPH. The associations between potential risk factors and the outcome were quantified by the OR and 95% confidence interval (CI). Multivariable logistic regression was performed to assess the relationship between patient characteristics and PPH.

RESULTS

The total number of patients that underwent C/S for PP was 227 during the study period. 57 patients were excluded for the reasons shown in Figure-1. There were 30 patients in the mild thrombocytopenia group and 140 patients in the control group. The total number of patients that underwent C/S for PP was 227 during the study period. 57 patients were excluded for the reasons shown in Figure-1. There were 30 patients in the mild thrombocytopenia group and 140 patients in the control group.

The baseline characteristics of the patients were listed in Table-1. There was no significant difference in terms of baseline characteristics between the two groups except preoperative platelet values.

The median preoperative platelet count was 136.000 in the mild thrombocytopenic group and 244.000 in the control group. Comparison of the groups in terms of obstetric outcomes was described in Table 2. There was no significant difference in gestational age at delivery, birth weight, PAS, underwent a hysterectomy, uterine balloon tamponade, and hospitalization in the ICU.

Figure-1 Selection of study groups

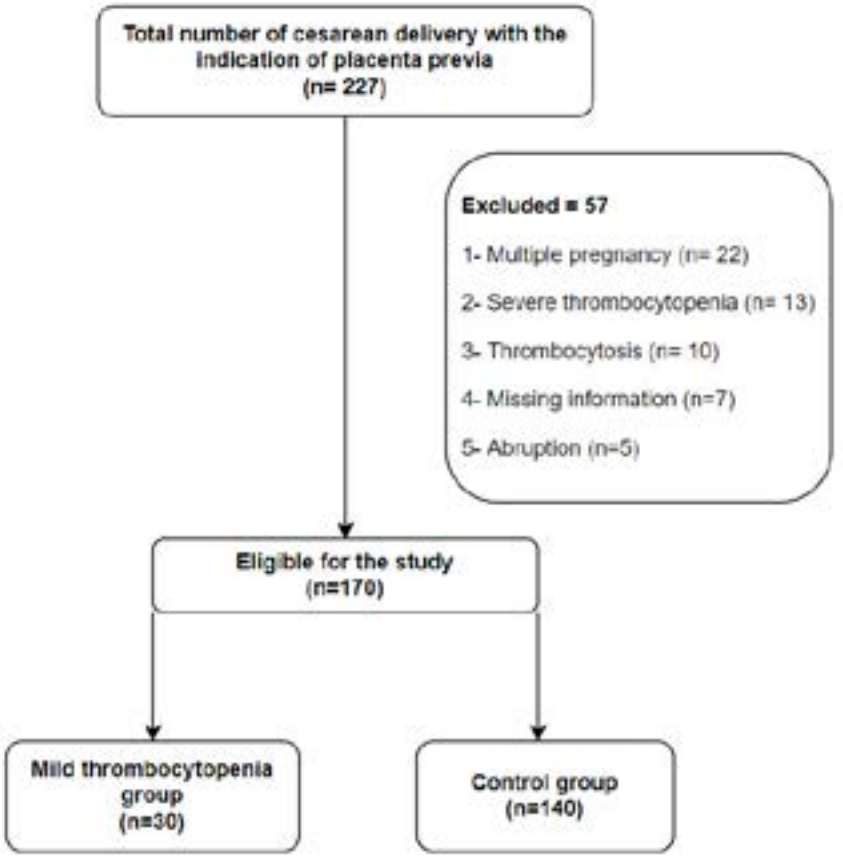

Table-1 Baseline Characteristics

	Mild thrombocytopenia group *(platelet count 100.000-149.999/ µl)* **(n= 30)**	**Control group (platelet count 150.000- 450.000 / µl) (n= 140)**	**p value**
Maternal age (years) (±SD)	31.5 (±4.8)	31.7 (±4.9)	0.908
Gravida, (median, IQR)	3 (2)	3 (2)	0.953
Primiparous, n (%)	6 (2)	28 (2)	1.000
Previous C/S, n (%)	22 (73.3)	83 (59.2)	0.151
Preoperative hemoglobin, g/dl (IQR)	11.9 (1.3)	11.5 (1.5)	0.061
Preoperative platelet count, 100.000/ µL (IQR)	136.000 (15.200)	244.000 (84.500)	**<0.001**

Data are presented as mean (± standard deviation), median (interquartile range) or number (percentage)
SD, standard deviation, *IQR*, interquartile range, *C/S*, cesarean section

Table-2 Comparison of the groups in terms of obstetric outcomes

	Mild thrombocytopenia group *(platelet count 100.000-149.999/ µl)* (n= 30)	Control group (platelet count 150.000- 450.000 / µl) (n= 140)	p value
Gestational age at delivery (week) (IQR)	35 (2.2)	36 (3)	0.572
Birth weight (gram) (±SD)	2586 (571)	2579 (647)	0.817
Placenta Accreata Sprectrum, n (%)	15 (50)	55 (39.2)	0.084
Hysterectomy, n (%)	9 (30)	38 (27.1)	0.137
Uterine balloon tamponade, n (%)	10 (33.3)	44 (31.4)	0.839
Hospitalization in the ICU, n (%)	7 (23.3)	24 (17.1)	0.426

Data are presented as mean (± standard deviation), median (interquartile range) or number (percentage)

IQR, interquartile range, *SD*, standard deviation, *ICU*, intensive care unit

As compared to the control group, PPH, the number of patients receiving pRCB, and Hb decline >3 g/dL were significantly higher in the mild thrombocytopenia group (Table-3).

Table-3 Outcomes of the study

	Mild thrombocytopenia group *(platelet count 100.000-149.999/ µl)* (n= 30)	Control group (platelet count 150.000- 450.000 / µl) (n= 140)	p value
PPH, n (%)	19 (63.3)	43 (30.7)	**0.001**
Patients received pRBC transfusion, n (%)	15 (50)	35 (25)	**0.006**
Hb decline >3 g/dL, n (%)	13 (43.3)	24 (17.1)	**0.002**

Data are presented as number (percentage).

PPH, postpartum hemorrhage, p*RBC*, packed red blood cell, *Hb*, Hemoglobin

In a multivariate logistic regression model, mild trombocytopenia was associated with PPH with an adjusted odds ratio (aOR) of 3.29 (95% CI 1.12-9.62 p=0.02) after adjusting for maternal age, gestational age at delivery, birth weight, preoperative anemia. PAS (aOR of 13.68, 95% CI 5.54-35.78), hysterectomy (aOR of 102.84, 95% CI 12.66-835.16), and previous C/S (aOR of 4.14, 95% CI 1.89-9.09) were also independent risk factors for the PPH (Table-4).

Table-4 Results of univariable analysis and multivariable logistic regression regarding the risk of postpartum hemorrhage

	OR (95% CI)	p value
Univariable analysis		
Maternal age	1.06 (1.00- 1.13)	0.44
Gestational age at delivery	1.03 (0.92-1.16)	0.52
Birth weight	1.00 (1.00-1.01)	0.37
Primiparous	3.26 (1.26-8.40)	**0.01**
Previous C/S	0.21 (0.10-0.45)	**<0.001**
Placenta Accreata Sprectrum	16.61 (7.24-38.11)	**<0.001**
Hysterectomy	107.00 (14.03-815.57)	**<0.001**
Mild thrombocytopenia	3.89 (1.7-8.89)	**<0.001**
Preoperative anemia	0.77 (0.39-4.52)	0.45
Multivariable analysis		
Mild thrombocytopenia	3.90 (1.56-9.72)	**0.003**
Placenta Accreata Sprectrum	13.68 (5.54-35.78)	**<0.001**
Hysterectomy	102.84 (12.66-835.162)	**<0.001**
Primiparous	0.37 (0.13-1.01)	0.06
Previous C/S	4.14 (1.89-9.09)	**<0.001**

OR, odds ratio, *CI*, confidence interval, *C/S*, cesarean section

DISCUSSION

In the present study, we aimed to investigate the relationship between mild thrombocytopenia and PPH in patients with PP. Our results are as follows: 1) Mild thrombocytopenia is associated with a higher rate of PPH, a significant decline in postoperative Hb, and a higher rate of blood transfusion in PP patients; 2) PAS, hysterectomy, and previous C/S were also found to be independent risk factors for PPH in PP patients.

In the present study, similar to the study of Attali et al. performed with elective C/S pregnancies, there were a higher rate of blood transfusion and a more significant decrease in postoperative Hb levels in the mild thrombocytopenia group (11). Carlson et al. also observed more PPH in the mild thrombocytopenia group in the study of 54597 pregnant women who underwent C/S or vaginal delivery after C/S (5). In a recent study with 1085 twin pregnancies, a group in which mild thrombocytopenia is prevalent, a significant relationship was found between mild thrombocytopenia and PPH (15). In our study, the rate of receiving blood transfusion was 50% in the mild thrombocytopenia group and much higher than in these three studies (in other studies the rate was 4.7%, 3.7%, and 5.7%, respectively. We consider that the difference is caused by a cohort with high bleeding frequency and amount such as placenta previa.

Govindappari et al. found that there was a 2-fold increase for the risk of PPH in the mild thrombocytopenia group among nulliparous women with term, singleton, vertex pregnancies. In this study, the need for blood transfusion did not increase. However, uterotonic usage was significantly higher in the mild thrombocytopenia group. This may have reduced the need for blood transfusions (7).

In the study of Işıkalan et al., although estimated blood loss was significantly higher in the mild thrombocytopenia group, there was no significant difference with regard to the blood transfusion rate between groups. However, this study was carried out only with healthy pregnant women who underwent elective C/S. In our study, there were both elective C/S and emergency C/S deliveries due to PP. Işıkalan et al. attributed the lack of difference in blood transfusion despite more bleeding to less preoperative anemia in the mild thrombocytopenia group. In our study, there was no difference between the preoperative Hb values of the groups (9).

Contrary to these findings, there are two studies in the literature that did not find a relationship between PPH and thrombocytopenia. Xu et al. performed their studies only with low-risk C/S deliveries (10). Alison DiSciullo et al. used unclear criteria for blood transfusion and more strict criteria for the diagnosis of PPH (Hb decrease by >4 g/dL) (8).

In order to reduce maternal morbidity and mortality, it is important to identify PPH risk factors before delivery. Plt <100.000 (according to some sources 70.000) is stated in the guidelines as a risk factor for PPH (2,5,6). In the group with a platelet value between 100,000-150,000, the PPH risk is uncertain. As shown by previous studies mild thrombocytopenia is seen much more frequently than severe thrombocytopenia, it is also important to take precautions in this group before delivery.

PP and PAS are obstetric conditions with a high risk of PPH. In this group, it is also important to determine the platelet threshold that can cause PPH. Our study identifies mild thrombocytopenia as a risk factor for PPH and blood transfusion for pregnant women with PP. Therefore, cautious hemostasis during the procedure, liberal use of uterotonic medicines, close monitoring for the identification of any deterioration, preparation of blood products before the delivery, and the use of multiple large IV cannulas could be advised in the group of PP with mild thrombocytopenia.

The strength of our study are having a large cohort for PP. While other studies about mild thrombocytopenia have used ICD criteria with high sensitivity but low specificity (16), we have used more certain criteria for PPH. Additionally, we minimized the effect of potential co-founders such as preoperative anemia by using two homogeneous groups. Besides, we excluded the effects of serious diseases such as ITP, HELLP, SLE on PPH by not including severe thrombocytopenia. Our study is limited by the fact that it was planned retrospectively and a single-center study. In addition, the lack of information about how much and how often these patients bleed during their pregnancy limits our study.

CONCLUSION

In conclusion, our study identifies mild thrombocytopenia as a risk factor for PPH and blood transfusion for pregnant women with PP. To define mild trombocypenia as a risk factor for PPH and blood transfusion in the general pregnant population, prospective observational studies with larger sample sizes and randomized controlled trials are required.

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Perinatal Outcomes in Hypoplastic Left Heart Syndrome

Hipoplastik Sol Kalp Sendromunda Gebelik Sonuçları

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ÖZ

Amaç: Prenatal olarak hipoplastik sol kalp sendromu (HLHS) tanısı konulan fetüslerdeki deneyimlerimizi gözden geçirmek.

Gereç ve Yöntem: Üçüncü basamak bir sevk merkezinde 2020-2022 yılları arasında prenatal olarak HLHS tanısı alan fetüslerin retrospektif çalışması.

Bulgular: 29 HLHS'li fetüs tespit edildi. 29 olgunun 13'ünde (%44,8) eşlik eden kardiyak anomaliler ve 8'inde (%27,5) eşlik eden ekstrakardiyak anomaliler vardı. Vakaların yalnızca küçük bir azınlığına (%20) invaziv tanı testleri uygulanmıştır ve bunların hepsinin karyotipi normaldir. Vakaların çoğu zamanında doğmuştur (%58,6), doğumdaki ortanca gebelik haftası 37 (dağılım, 34-39) ve ortalama standart sapma doğum ağırlığı 3099±455 gramdır. Ayrıca, HLHS erkek fetüslerde kız fetüslere göre daha yaygındı (%69'a vs %31). Tanı konulan 29 vakanın 4'ünde (%13,7) gebeliğin sonlandırılması seçilmiş ve ≤ 26. gebelik haftasından önce gerçekleştirilmiştir. Gebeliğin 23,29 ve 34. haftalarında 3 intrauterin fetal ölüm (IUFD) gerçekleşmiştir. 29 HLHS vakasının 22'si (%75,8) canlı doğmuştur. Canlı doğan 22 bebekten 3'ü uygun cerrahi adayları olmadıkları için tıbbi prosedürlerle tedavi edilmiş ve daha sonra postnatal 22., 23. ve 25. günlerde ölmüştür. Olguların 15'ine cerrahi uygulanmış olup bunlardan sadece biri halen hayattadır. Yenidoğan döneminin ilk üç ayındaki mortalite oranı %96.5 idi.

Sonuç: Fetal ekokardiyografi, ilk trimesterın sonlarından itibaren HLHS'nin kesin tanısının konulmasına olanak sağlamaktadır. Erken prenatal tespit ve postnatal cerrahi müdahalelere rağmen, merkezimizin son iki yıldaki bulguları, HLHS için kötü sonuçları yansıtmaktadır.

Anahtar Kelimeler: hipoplastik sol kalp sendromu; prenatal; postnatal; sonuç; fetüs

ABSTRACT

Aim: To review our experience in fetuses with prenatally diagnosed hypoplastic left heart syndrome (HLHS).

Materials and Method: Retrospective study of fetuses prenatally diagnosed with HLHS between 2020 and 2022 in a tertiary referral center.

Results: 29 fetuses with HLHS were identified. 13 of all 29 cases (44.8%) had associated cardiac abnormalities and 8 cases (27.5%) had coexisting extracardiac abnormalities. Only a small minority of cases underwent invasive diagnostic testing (20%), and all of which had a normal karyotype. Most cases were delivered at term (58.6%), median gestational week at delivery was 37 (range, 34-39), and the mean standard deviation (SD) birthweight was 3099±455 grams. In addition, HLHS was more common in male than in female fetuses (69% vs 31%). Termination of pregnancy (TOP) was selected in 4 (13.7%) of the diagnosed 29 cases and performed before at ≤ 26 weeks of pregnancy. There were 3 intrauterine fetal demise (IUFD) at 23,29, and 34 weeks of gestation. Among the 29 cases of HLHS, 22 (75.8%) were live born. 3 of 22 live born infants were managed by medical procedures as they were not appropriate surgical candidates and later died at 22nd, 23rd and 25th of postnatal day. Surgery was performed in 15 cases and only one of them is are still alive. Mortality rate in the first three months of neonatal period was 96.5%.

Conclusion: Fetal echocardiography allows an accurate diagnosis of HLHS, which is made even

in the late first trimester. Despite early prenatal detection and postnatal surgical interventions, the results from our center in last two years reflect poor outcomes for HLHS.

Keywords: hypoplastic left heart syndrome, prenatal, postnatal, outcome, fetus

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INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is one of the most severe forms of congenital heart disease, one of the most difficult to treat, and incompatible with life if left untreated. The prevalence of HLHS in the United States is approximately 2 to 3 cases per 10,000 live births and accounts for 2 to 3 percent of all congenital heart diseases (1, 2). The reported incidence is most probably underestimated because the number of spontaneous abortions and terminations of affected fetuses is indeterminate. It is characterized by underdevelopment of the left-sided structures of the heart, which include the mitral valve, left ventricle, aortic valve, and aortic arch, resulting in inadequate support of systemic perfusion. However, the fetus diagnosed with HLHS is very stable, and death in utero is uncommon, but when it does occur, it is often associated with a genetic or chromosomal abnormality. In fetal HLHS, the developed right ventricle usually functions well, providing a combination of placental umbilical venous return and fetal systemic venous return via the fetoplacental circulation.

The vast majority of HLHS cases are detected prenatally by fetal echocardiography, which provides an opportunity for counseling and perinatal planning and also allows prenatal counseling of the family and preparatory planning for delivery and postnatal care by the obstetric and cardiology team. On fetal echocardiography, HLHS is typically characterized by hypoplasia of the left ventricle with mitral atresia or stenosis, aortic atresia or stenosis, and hypoplasia of the ascending aorta.

Despite prenatal diagnosis, counseling, and improved postnatal surgical and medical interventions, mortality and morbidity remain high in our country. Therefore, the aim of this study was to present our experience with prenatally diagnosed HLHS in terms of associated anomalies, neonatal outcomes, and mortality rates to gain experience for future fetal and neonatal interventions.

MATERIALS AND METHOD

We retrospectively analyzed all cases of HLHS diagnosed between 2020 and 2022 at our tertiary referral center for prenatal diagnosis and management of fetal and neonatal disorders during pregnancy. This retrospective study was approved by the local Institutional Review Board (E2-23-3488). We searched our computerized database for prenatally diagnosed HLHS and also performed a literature search to compare our data with those of previous series.

Ultrasound examinations were performed with a Voluson E10 system (GE Healthcare Medical Systems, Milwaukee, WI, USA) and included detailed assessment of cardiac and noncardiac structures according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines (3). Fetal heart examinations were performed with conventional two-dimensional ultrasound and color and pulse-wave Doppler ultrasound by fetal cardiologists and obstetricians specializing in prenatal diagnosis and fetal echocardiography. Prenatal diagnoses were made with the constellation of anatomic findings for HLHS (diminutive LV, abnormal mitral and aortic valves, and a hypoplastic ascending aorta). The diagnoses were confirmed by postnatal echocardiography performed by experienced pediatric cardiologists in liveborn infants during neonatal stay or from autopsies in stillbirths or termination.

According to the definition of the International Nomenclature Society (4), hearts with hypoplasia of the left ventricle with transposition of great arteries (TGA) or double outlet right ventricle (DORV), or with a common atrioventricular septal defect (AVSD), should be excluded. In addition, examination of large series of hearts from pathology archives has confirmed that the integrity of the ventricular septum is one of the most obvious features of HLHS (5, 6). Therefore, we excluded the 9 cases including ventricular septal defect (VSD), and also hypoplastic left ventricle cases due to either transposition or double outlet right ventricle, or with a common atrioventricular junction were also excluded from our study. All pregnant women with early detected fetal HLHS were advised to undergo fetal karyotyping.

To perform this study, the following variables were evaluated: Maternal age, gravidity, parity, previous miscarriage, living child, gestational week at diagnosis, presence of associated cardiac and extracardiac abnormal findings, gestational age at delivery, neonatal sex, birth weight, Apgar scores at the first and fifth minutes, postnatal surgical and medical interventions and follow-up, mortality due to HLHS, and short-term outcomes.

Statistical analysis

Data were collected using an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA). For statistical analysis, continuous variables were presented as mean and standard deviation (SD) or median and range values according to the normally distribution by using the Kolmogorov–Smirnov test. Categorical variables were presented as numbers and percentages.

RESULTS

During the 2-year period of the current study, 38 pregnancies were evaluated and of the 38 cases complicated by fetal HLHS during the study period, 9 cases were excluded from further analysis: 5 with a coexistent VSD, 2 DORV, 2 AVSD, because we suggest that lesions to be included in HLHS should have an intact ventricular septum. Finally, we included 29 cases in the study analysis.

The characteristics of the study population is presented in Table 1. The mean standard deviation (SD) of maternal age was 27.07±6.50 years and the median (min-max) gestational age at diagnosis of HLHS were 25 (14-38) weeks. Table 1 also outlines the associated cardiac and extracardiac abnormal findings of HLHS cases on the basis of prenatal sonographic appearance. 13 of all 29 cases (44.8%) had associated cardiac abnormalities and 8 cases (27.5%) had coexisting extracardiac abnormalities as detailed in Table 1. According to prenatal sonographic findings, isolated HLHS occurred in 14 (48%) of cases.

First trimester screening was performed in only 12/29 (41%), and 11 cases were reported as low combined risk. Although all pregnant women with early detected fetal HLHS were advised to undergo fetal karyotyping, only a small minority of cases underwent invasive diagnostic testing (20%), and all of which had a normal karyotype.

Table 1. Characteristics and ultrasound findings of 29 fetuses with a prenatal diagnosis of hypoplastic left heart syndrome (HLHS)

	HLHS (n=29)
Maternal age (mean, SD)	27.07±6.50
Gravidity (median, min-max)	2 (1-5)
Parity (median, min-max)	1 (0-3)
Previous miscarriage (median, min-max)	0 (0-2)
Living Child (median, min-max)	1 (0-3)
Gestational week at diagnosis (median, min-max)	25 (14-38)
Diagnosis before 24 weeks of pregnancy (n, %)	13 (44.8%)
Associated cardiac findings (n, %) • Atrial septal defect • Tricuspid regurgitation • Pericardial effusion • Persistent left superior vena cava • Partial anomalous pulmonary venous return • Right isomerism • Supraventricular tachycardia	13 (44.8%)

Table 2 and Table 3 summarize the fetal and neonatal outcomes of all cases with a prenatal diagnosis of HLHS. Most cases were delivered at term (58.6%), median gestational week at delivery was 37 (range, 34-39), and the mean standard deviation (SD) birthweight was 3099±455 grams. In addition, HLHS was more common in male than in female fetuses (69% vs 31%). Termination of pregnancy (TOP) was selected in 4 (13.7%) of the diagnosed 29 cases and performed before at ≤ 26 weeks of pregnancy (Table 3). There were 3 intrauterine fetal demise (IUFD) at 23,29, and 34 weeks of gestation (Table 3).

Table 2. Fetal and neonatal outcomes of fetuses with a prenatal diagnosis of HLHS

	HLHS (n=29)
GA at delivery (median, min-max)	37 (34-39)
Term delivery (n, %)	17 (58.6)
Preterm birth (n, %)	5 (17%)
Birth weight (grams) (mean, SD)	3099±455
Gender (n, %) Male Female	 20 (69%) 9 (31%)
Apgar at 1st minute (median, min-max)	6 (1-7)
Apgar at 5th minute (median, min-max)	8 (3-9)
Mode of delivery (n, %) • Caesarean section • Vaginal delivery	 18 (62%) 11 (38%)
Short term outcome (n, %) • Termination of pregnancy • Intrauterine fetal demise • Live Birth • Mortality	 4 (13.7%) 3 (10.3%) 22 (75.8%) 28 (96.5%)
Management of live births (22/29) • Death before surgery • Death after surgery • Alive after surgery • Not suitable for surgery (medical palliation)	 5/22 14/22 1/22 3/22

Table 3. Characteristics and outcomes of 29 fetuses with a prenatal diagnosis of HLHS

Case	GW at diagnosis	Associated cardiac findings	Associated extracardiac findings	Gender	GW at birth Birth weight	Perinatal outcome
1	37	ASD, TR	SGA	Female	38-2320	Live birth, PN day 12 ex after BAS, Norwood
2	37	-	-	Male	39-3200	Live birth, PN day 23 ex after PB
3	32	-	-	Female	36-3520	Live birth, PN day 0 ex
4	38	ASD, PE	-	Male	38-3680	Live birth, PN day 2 ex after Norwood
5	26	-	-	Male	37-2470	Live birth, PN day 71 ex after PB
6	21	TR	-	Male	24-560	TOP
7	32	TR, PLVCS	SUA, VM, CH	Female	34- 2050	IUFD
8	32	ASD, TR, PAPVR		Male	37-3360	Live birth, PN hour 12 ex after BAS
9	23	ASD	-	Female	39-3300	Live birth, PN day 12 ex after PB
10	32	-	-	Male	38-3140	Live birth, PN day 12 ex after BAS
11	24	-	-	Male	36-2400	Live birth, PN day 10 ex after PB
12	21	ASD, TR		Male	37-3230	Live birth, PN day 11 ex after Norwood
13	23	-	-	Female	39-3860	Live birth, PN day 0 ex
14	37	ASD, TR	-	Male	38-3600	Live birth, PN month 9 ex after Norwood Sano shunt
15	22	PLVCS	SGA	Male	38-2780	Live birth, PN day 2 ex after Norwood
16	22	-	-	Female	26-300	TOP
17	14	-	-	Male	38-3350	Live birth, **18 months alive after PB and Glenn**
18	22	-	SGA	Female	38-2465	Live birth, PN day 22 ex after medical palliation
19	26	-	-	Female	38-3100	Live birth, PN day 11 ex before surgery
20	23	ASD, PAPVR, SVT	Club foot	Male	37-3080	Live birth, PN day 11 ex before surgery
21	33	-	-	Male	36-3370	Live birth, PN day 7 ex after PB
22	34	-	-	Male	38-2480	Live birth, PN day 15 ex after PB
23	36	ASD	-	Female	36-3640	Live birth, PN day 23 ex after medical palliation
24	22	Right isomerism	CCA, VM	Male	26-1060	TOP
25	31	-	-	Male	38-3560	Live birth, PN day 25 ex after medical palliation
26	21	-	SGA	Male	39-2540	Live birth, PN day 5 ex after Norwood
27	26	-	-	Male	29-1300	IUFD
28	21	-	-	Male	22-260	TOP
29	21	TR	VM	Male	23-740	IUFD

ASD, atrial septal defect; TR, tricuspid regurgitation; GW, gestational week; HLHS, hypoplastic left heart syndrome; IUFD, intrauterine fetal demise; IUGR, intrauterine growth restriction; SGA ,small for gestational age; gr, grams; ex, exitus; PND, postnatal; BAS, balloon atrial septostomy, TOP, termination of pregnancy; PLVCS, persisted left vena cava superior; SUA, single umbilical artery; VM, ventriculomegaly; PAPVR, partial anomalous pulmonary venous return; pulmonary banding, PB; SVT, supraventricular tachycardia; CCA, corpus callosum agenesis; CH, cerebellar hypoplasia; PE, pericardial effusion

mong the 29 cases of HLHS, 22 (75.8%) were live born. 3 of 22 live born infants were managed by medical procedures as they were not appropriate surgical candidates and later died at 22nd, 23rd and 25th of postnatal day. Surgery was performed in 15 cases and only one of them is are still alive. He is 18 months old, and bilateral pulmonary banding and subsequent Glenn procedures was performed him. Mortality rate in the first three months of neonatal period was 96.5%.

DISCUSSION

The present study has shown that, unfortunately, our postnatal outcomes in last two years have been extremely poor and far from recent literature (7, 8), and HLHS seems to be the main cause of death, regardless of additional extracardiac, cardiac and chromosomal abnormalities. We have not included cases of HLHS associated with some complex cardiac anomalies (especially those with VSD) in the study to maintain a homogeneous group. Although there is no universal opinion on whether routine ultrasonography can alter outcome, fetal echocardiography allows early diagnosis of HLHS and gives clinicians the opportunity to triage this group depending on prenatal findings. Our data also suggest that HLHS is increasingly diagnosed in utero, in agreement with the literature (7). Although postnatal surgical outcomes in HLHS have steadily improved, significant morbidity and mortality are common (9). Through improvements in fetal diagnosis and innovations in interventional techniques, there is an increasing interest in surgical interventions for a variety of congenital diseases in utero, including spina bifida, congenital diaphragmatic hernia, tumors, and congenital heart disease (10). In some forms of HLHS, fetal aortic stenosis during gestation leads to endocardial fibroelastosis and in utero progression of aortic stenosis to HLHS. Fetal aortic balloon valvuloplasty increases blood flow through the left heart and decreases left

ventricle pressure load and prevents progression to HLHS (11, 12). Fetal cardiac interventions alter the disease progression and may potentially improve our postnatal outcomes. Therefore, future high-risk cohort studies are needed.

In our study, HLHS predominated in males (69% vs. 31%), which is consistent with most population-based and clinical studies (13, 14). A previous multicenter study between 2003 and 2014 showed that the presence of Turner, DiGeorge, and Down syndromes was associated with increased mortality and morbidity in infants with HLHS (15). However, although all the pregnant women with early detected fetal HLHS were recommended to undergo fetal karyotyping, only a small minority of cases (20%) underwent invasive diagnostic testing, and all of these women had a normal karyotype.

The presence of HLHS is often suspected or can be readily diagnosed by an obstetrician at the 20 weeks pregnancy obstetric ultrasound owing to the great distortion in the 4-chamber view whether or not the presence of associated cardiac, extracardiac and chromosomal abnormalities. However, in only 44% of cases, the diagnosis was made before the 24th week of pregnancy, which is lower than the observations of previous studies (16, 17). This is due to the fact that our clinic is a referral center, and not a primary follow-up.

In the present study, approximately 27.5% of associated extracardiac and 44.8% of cardiac defects were detected. Despite the frequency of extracardiac abnormalities in the literature ranges between 3% and 62% (7, 18, 19), our results are consistent with the majority of outcome studies(20). Song et al. reported in a multicenter study that isolated HLHS occurred in 62.8% of cases (21) . However, Tennstedt et al. reported that isolated HLHS was found only 38% of fetuses examined by autopsy (22), and Wojtowicz et al. reported 40% isolated HLHS (17), which is consistent with the present study, in which isolated HLHS occurred in 48% of our cases.

Our study has several limitations. The main limitations of the present study are the relatively small sample size and the retrospective design. Namely, we conducted an institutional rather than a population-based study that included a small number of fetuses with HLHS. In addition, as mentioned previously, large series from literature have confirmed that the integrity of the ventricular septum is one of the most obvious features of HLHS (5, 6). Therefore, because we also excluded the cases including VSD, our sample size was even smaller compared to studies with included (17).

CONCLUSION

Fetal echocardiography allows an accurate diagnosis of HLHS, which is made even in the late first trimester. Despite early prenatal detection and postnatal surgical interventions, the results from our center in last two years reflect poor postnatal outcomes for HLHS. To improve postnatal outcomes, we hope that our study will contribute to the more frequent use of fetal cardiac interventions in clinical practice than ever before.

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Who Are Anesthesiologists After The Covid-19 Pandemic? Evaluation Of Public Awareness About Who Are Anesthesiologists?

Covid-19 Pandemi Sonrasinda Anestezistler Kimdir? Anestezistler Hakkinda Halkin Bilinçlilik Durumunun Değerlendirilmesi

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ÖZ

Amaç: Coronavirüs 2019 (COVID-19) hastalığından önce yapılan çalışmalarda, anestezistlerin ameliyathane içinde ve dışında görev ve rollerinin halk tarafından tam olarak bilinmediği görülmüştür. Bu çalışmada amacımız Türkiye'de COVID-19 pandemi sonrasında halkın gözünden anestezistlerin görevlerinin bilinip bilinmediği ölçülecektir.

Gereç ve yöntem: Çalışmada, 24 soru içeren bir anket, birçok farklı online platformlarla 16 yaşından büyük ve herhangi bir sağlık sektörüyle ilgisi olmayan halka sorulacaktır.

Bulgular: 2222 kişi anketi cevapladı ve yalnızca %37,6 'sı anesteziolojistlerin yoğun bakımda hasta takip ettiğini bilmiş ve ayrıca %68,4 cevaplayıcı ise anesteziyolojinin bir tıbbi uzmanlık olduğunu bilmiştir. %82,1 cevaplayıcı ise pandemi sırasında hastalarının hangi branş hekimi tarafından yoğun bakımda takip edildiğini bilememiştir. Cevaplayanların %59,9 gibi büyük bir kısmı COVID-19 pandemi sonrasında anesteziyolojistlerin görevleri hakkında bir düşüncelerinde bir değişiklik olmadığını bildirmişlerdir.

Sonuç: Çalışma anket cevaplayıcıları arasında eğitim seviyesi arttıkça, sağlık sistemi hakkında

daha çok bilgi sahibi olunduğunu ve Türkiye'de anesteziyolojistlerin görevlerinin pandemi sonrasında halen anlaşılamadığı görülmüştür. Bu çalışma, anesteziyolojistlerin görevlerinin halk tarafından daha iyi bilinmesi için daha fazla çalışma yapılması gerektiği gösterilmiştir.

Anahtar kelimeler: COVID-19, SARS-CoV-2, anestezi, anesteziyolojist, yoğun bakım, ağrı

ABSTRACT

Aim: Previous research has demonstrated that the general perception of the expertise and responsibilities of anesthesiologists, both in and out of the operating room, is unclear, before the onset of COVID-19. This study aims to evaluate the perception of the public regarding the role of anesthesiologists after the COVID-19 pandemic in Turkey.

Materials and Methods: For this study, an online survey was conducted using a random selection method across various online platforms. The survey was directed to individuals who were not associated with the healthcare industry or any medical activity and were 16 years or older. The survey consisted of 24 questions. The questionnaire is divided into three parts. The first part collects data on demographics. The second part assesses knowledge related to anesthesia procedures. The third section emphasizes information regarding the role of the anesthesiologist.

Results: The questionnaire was completed by 2222 participants, and only 37.6% of them were aware that anesthesiologists also follow patients in intensive care. Regarding the COVID-19 pandemic, 82.1% of the respondents were uncertain about which physician was in charge of treating patients in the intensive care unit (ICU). The fact that anesthesiologists are medical specialists was known to only 68.4% of the participants. About 59.9% of the participants did not observe any change in their perception of the anesthesiologist's role after the onset of the COVID-19 pandemic.

Conclusion: The study concluded that even though participants had higher educational levels and there was increased public awareness of the healthcare industry during the pandemic, the Turkish public still held inaccurate perceptions regarding the role of anesthesiologists. Efforts should be made to better inform the public about the roles of anesthesiologists.

Keywords: COVID-19, SARS-CoV-2, anesthesia, anesthesiologist, intensive care unit, pain,

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INTRODUCTION

William T. G. Morton administered anesthesia publicly for the first time in 1846. Anesthesiology introduced itself to the non-medical world at the 1939 New York World's Fair (1). Anesthesiology was recognised as a specialty in Turkey in 1956. Anesthesia and anesthesiology made significant progress thereafter and evolved into one of the major branches of medicine. Currently, anesthesiologists have critical responsibilities both in the intensive care units, pain clinics, and operating rooms.

Surveys conducted in the past 25 years have shown that the percentage of patients who were aware of the anesthesiologist's role in the medical field and the anesthesia procedure varied from 50 to 95%.

The anesthesiologist's leadership in the intensive care units during the COVID-19 pandemic was recognized. However, in a pre-pandemic study, the role of anesthetists in the ICU was reported to be 53.4%, while another study found that only 13.5% viewed anesthesiologists as being involved in the management of critically ill patients (13-14). In yet another study conducted in Turkey by Ezgi et al. (15), 37.4% of the patients were aware of the anesthesiologist's role in the ICU.

After all these studies, increasing awareness of the role of anaesthetists can be achieved through enhanced patient-physician communication and media coverage of their responsibilities. Following intensive care treatment of many patients and the contribution of numerous anaesthetists during the war, with media statements by authorized doctors and everyone learning the word 'intubated', we sought to explore whether the responsibilities and duties of the 'secret hero' anaesthetist had improved in the eyes of the public for the first time since the COVID-19 pandemic.

This study aimed to evaluate public perception of the role of anesthesiologists in Turkey after the COVID-19 pandemWe conducted a prospective, cross-sectional survey between February and April 2022. The Ankara City Hospital Ethical Committee (E1-21-2118) and Clinical Trials NCT05741320 approved the study. Inclusion criteria for the study were individuals aged 16 or above with no involvement in the healthcare or medical professions.

The study's size was determined by reviewing existing data, as is common practice. The questionnaire was modelled on previous research to enable result comparison (10).

We prepared a questionnaire to survey the public about COVID-19, including 5 questions based on current literature (see Appendix). The questionnaire was posted on the Google Survey platform. We randomly distributed the link to the form (https://forms.gle/WuYuDjUG7PDreJyr5) via email and social media platforms.

The questionnaire consists of three parts: the first part contains demographic data, including questions about sex, age, education, occupation and previous hospital, surgical and anaesthetic experience. The second part consisted of questions that tested the knowledge of anesthesia procedures and required identification of the anesthesiologist, including their place of work. What are the responsibilities of anesthesiologists after surgery? And the respondents had to answer with either 'yes', 'no', or 'I don't know.' The final section of the questionnaire analysed COVID-19 and ICU follow-up experiences. Participants were asked about their infection status, if they had been hospitalized in an ICU due to COVID-19, and if they knew the specialist who had treated them in the ICU.

Participants completed the questionnaires online, and the responses were recorded in the Google Survey database for analysis. The data is presented as numbers and percentages.

METHOD

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Participants completed the questionnaires online, and the responses were recorded in the Google Survey database for analysis. The data is presented as numbers and percentages.

RESULTS

he questionnaire was responded to by 2222 individuals, among whom 73.5% were female and 26.5% male. 83.3% of the people belonged to the age group 30-64 years; 12.1% belonged to the age group 18-29 years; and 4.6% were older than 65 years. The study found that 76.7% of participants held a university degree, and 40.2% were employed in the private sector. (Table 1)

Table1: Demographic data of respondents

Gender (Male/Female, %)	26.5/ 73.5
Age (18-29/ 30-64/ 65) (%)	12.1/ 83.3 /4.6
Previous anesthesia (%)	
No	18.6
Yes	81.4
Education (%)	
Primary	1
Secondary	2
High school	20.3
University	76.7

A total of 74.4% of the participants had previous hospitalization experience, with 73.4% of the participants having undergone surgery before. Anesthesia history was reported by 81.4% of the participants, with 79.9% of them having experienced general anesthesia before.

In 68.4% of respondents, the anaesthetist was the person who administered the anaesthesia and in 35% of cases, the anaesthesia technician was the person who administered the anaesthesia. When asked, "Who is an anesthesiologist?" Out of the respondents, 71.2% were identified as anesthesiologists, 4.5% as someone in the hospital trained as anesthesiologist, 4.5% as nurses and 3.7% as unqualified doctors.

Regarding the anesthesiologist's work environment, 98.8% of the respondents mentioned the operating room, while only 1.2% were uncertain. When asked about the duties of an anaesthetist beyond the operating room, only 37.6% of the respondents were aware of their responsibility for patients in the ICU, while 24.7% were unaware. A total of 46.5% of respondents answered "yes" when asked if the anaesthetist was responsible for post-operative pain management in the post-operative care unit.

When asked about the duties and responsibilities of the anaesthesiologist during the operation, 97.8% of responders answered as follows: to follow the patient's awareness and consciousness. During surgery, 68.5% of respondents stated that the anaesthetist controls blood pressure and heart rate; 22.8% estimated and transfused serum and blood during surgery; 44.8% replied that the anaesthetist does nothing; 32.4% replied that they don't know. During surgery, 87.2% of the respondents indicated that they control patients' pain, while 39% treat postoperative nausea and vomiting. Furthermore, 46.5% of the respondents reported controlling the patients' pain at the end of the surgery. (Table 2)

Table 2: Responders' answers of an anesthesiologist's role

	Yes	No	I don't know
In operating room	98.8		1.2
In ICU	37.6	37.7	24.7
Labor anesthesia	84.8	6.2	10.6
Pain clinic	46.6	23.5	29.9
Makes surgery	2.45	89.6	7.9
Emergency Position	67.1	12.8	20.1

When asked who was responsible for postoperative care in the anaesthesia care unit, 51% said the anaesthetist, 38.5% said the surgeon and anaesthetist together, 4.2% said the surgeon alone and 6.3% said they don't know.

Another question asked whether the respondents were afraid of anaesthesia. And 50.6% said "no", 43.4% said "yes" and 6% said "don't know". A further question analysed the fear of anaesthesia, and 33.3% of the answers were not waking up from anaesthesia, 9.5% will not sleep completely, 17% will wake up, and 17% will feel pain during the operation; the 23.1% answer was all of these.

Questions about COVID-19 were asked at the end of the survey. The first question was "Have you had a COVID-19 infection" and only 12.8% answered yes. The second question was "Have you had a patient followed up in intensive care for COVID-19?" and 25% answered yes. And if they know who followed their patient in the ICU, the answer is 17.9% yes.

Another question was: Which medical specialties can be trained to become an intensive care specialist? 47% of respondents answered all specialties: 32.4% answered anaesthesia, 32.2% surgery and 8.6% ophthalmology. When asked if the roles and responsibilities of anaesthetists were better understood after the COVID-19 pandemic, 59.9% did not know, 25.6% yes and 14.5% no.

DISCUSSION

Despite the high risk of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), anaesthetists around the world continued to be at the forefront, maintaining a tradition of ingenuity and dedication. With this study, we wanted to find out whether the role of "undercover hero" continues for the public, and whether the public's perception of the role of the anaesthesiologist has changed since the COVID-19 pandemic for the first time with more than 2000 randomly selected participants. In our study, unfortunately, we found that not much has changed: only 71.2% of the respondents knew that anaesthetists are medical specialists; 68.5% monitored haemodynamic parameters during surgery; only 22.8% answered the question about the assessment and transfusion of serum and blood during surgery by the anaesthetist and 44.8% by the surgeon; the control of post-operative nausea, vomiting and pain after surgery was answered by only 39 and 46% respectively. The most important finding of our study after the two-year pandemic period was that 63.4% of respondents still did not know the role and responsibilities of the anaesthetist in the ICU.

Anesthetists' image and status have long been a source of contention in the medical community and the public. In the literature, a lot of studies can be found before the COVID-19 pandemic, about poor knowledge of who the anesthesiologist

was, what his or her duties and responsibilities were. At the conclusion of all these studies, it was stated that more individual efforts by anesthesiologists, media, and health programs must be needed.

In the studies conducted in the literature about this subject, the correct answer to the question of who an anesthesiologist was varied between 50 and 99%, and our findings were similar to these studies. (2-12)

When we looked at the two studies that were performed in Turkey before the pandemic, the first one by Ezgi et al., they found 66.3% of the people knew the anesthesiologists were specialists, similar to our results, even though their responder's education level was lower than in our study. (15) And similar to our study, they found that 37.4% of responders knew the anesthesiologists worked in the intensive care unit. In the second study, Sagun et al, 76.3% of the patients knew that an anesthesiologist is a medical specialist, but unlike our study, only 4% of respondents knew that anesthesiologists worked in ICUs. (16) The difference between these two studies and ours is that the first enrolled in 1994, whereas the second enrolled only 250 preoperative patients. We tried to analyze a heterogeneous, randomly selected population, not some specific patient population who were not linked with anesthesia and were not awaiting surgery. With this approach, we believe that we can better reflect society and yield more objective results.

In another study, whose protocol was similar to ours from Romania before the COVID pandemic, 92.9% of the responders knew who the anesthesiologist was, but only 32% knew their role in the ICU. They explained their results with education level that was lower than those in our study (10). But just like our study with Shevde et al. and the last study before the pandemic in 2022 by Arefayne et al. showed, there is no correlation between anesthesia knowledge and educational level (13,17).

We can see that a lot of factors, like age, gender, education level, and responder population, affect the knowledge in the literature. In the study of Arefayne et al., 53.4% of the responders knew that anesthesiologists worked in ICUs, but their respondents were only preoperative patients, and their education level was 35.8% illiterate (13).

When the anesthesiologist's duties were analyzed, we found that 44.8% of respondents thought serum and blood transfusions during surgery were made by the surgeon and postoperative pain and postoperative nausea and vomiting were not controlled by an anesthesiologist for 49% and 61%, respectively. These results mostly corroborate a lot of studies (18,19). Deepa et al. found similar or even worse results about the patients maintaining hemodynamics during the operation: less than 5% (20). Also, Onutu et al. found similar results to ours; in their study, they found that 36.2% of patients had estimated bleeding and made blood and serum transfusions by an anesthesiologist, and 54.6% of postoperative pain was controlled by the surgeon (10).

Finally, while anesthetists fulfill many roles outside the operating room, especially in intensive care units, these roles are very rarely ascribed to anesthetists by the public. In the literature, we can find that there is poor knowledge about the roles of anesthesiologists in ICU before the COVID-19 pandemic. The pandemic has been an opportunity for anesthesiologists to showcase their skills. These skills were used successfully in the process of distributing care in the COVID-19 pandemic, both to COVID and non-COVID patients. For the moment, we have the attention of the entire hospital and much of the general public, or at least that's what we anesthesiologists thought. Before the pandemic, the knowledge of the anesthesiologist's role in the ICU was between 6–40% (10,13,15,16).

The COVID-19 pandemic should be a wakeup call, but in our study, we found that, nothing had changed; only 37.6% of the people knew that anesthesiologists had a role in ICUs after the two years of the pandemic. Unfortunately, the question of "I know the duties of an anesthesiologist better after the COVID-19 pandemic?" was answered I didn't notice" by 59.9%.

We thought that the COVID pandemic generated public awareness about anesthesia and the role of an anesthesiologist in ICU. Even the scope and versatility that anesthesiologists demonstrated during the COVID-19 pandemic and made daily routine practice "the secret hero identity" didn't change. There can be a lot of reasons for inadequate knowledge.

1. It doesn't matter to them who was following their patients. This is so much related to age, gender, educational status, personality, and socioeconomic status, which we mentioned earlier. Further education for the public of the diverse roles and responsibilities of the anesthesiologists would be invaluable in promoting the importance of our work.

2. The anesthesiologist's identity as intensive care workers is lagging; however, when asked, the underlying identity is stated. Although even the head of the intensive care association is an anesthesiologist in our country, everybody knows him as an intensive care specialist, the identity of the anesthesiologists has remained hidden behind the identity of the intensive care.

3- Changing teams of anesthesiologists routinely during a working day means that patient relatives are seen by different anesthesiologists every time, and this could be a factor in creating confusion. So, people were unaware of whom they were meeting.

In conclusion, the results show a poor perception of the anaesthetist and his responsibilities, which are still poorly understood after a great pandemic. As Papper stated in 1950, "many physicians are completely unaware of the knowledge that the anaesthesiologist possesses" (21). We must earn the right to do so by gaining the respect of our colleagues in medicine, the public and management. This can be improved by developing the anaesthesiologist-patient relationship, and more efforts should be made to inform the public correctly about the activities and responsibilities of anaesthesiologists.

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Polikistik Over Sendromunda klomfen sitrata dirençli vakalarda ikincil tedavi olarak laparoskopik ovarian drilling kullanımı

Evaluation of laparoscopic ovarian drilling and pregnancy outcomes as a secondary treatment in Polycystic Ovary Syndrome

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ÖZ

Giriş: Polikistik over sendromu (PCOS), üreme çağındaki kadınlarda %6-21 ve anovulatuar infertilite tanısı almış hastalarda yaklaşık %90'lık prevalansı olan çok yaygın bir over endokrinopatisidir. PCOS'lu hastalarda anovulatuar infertilite için, laparoskopik over drilling (LOD), klomifen sitratın başarısızlığından sonra ovulasyon indüksiyonu için başarılı bir ikinci basamak tedavi olarak kullanılmaktadır. Biz bu çalışma ile klomifen sitrata dirençli PKOS olgularında LOD ve gonadotropinlerin gebelik elde etme üzerindeki etkisini belirlemeyi ve karşılaştırılan parametrelerden hangilerinin canlı doğum oranına olumlu etkisi olduğunu göstermeyi amaçladık.

Materyal-metod : Haziran 2017 ile Aralık 2019 tarihleri arasında, polikistik over sendromlu toplam 145 klomifen sitrata dirençli gönüllü katılımcı çalışmaya dahil edildi. Hastalar iki gruba ayrıldı ; 56 hastaya laparoskopik over drilling uygulandı , 89 hastaya ise 6 aylık süre içinde en fazla 2 kez gonadotropin ile low doz step-up protokolü ile indüksiyon yapıldı. Gonadotropin ile indüksiyon sonrası recombinant hcg ile ovulasyon tetiklendi ve zamanlı coit önerildi. Laporoskopik ovaryan drilling yapılan hastalar ise 6.yın sonunda değerlendirmeye alındı . Her 2 grup 6.ayın sonunda laboratuar parametreleri ve gebelik sonuçları açısından kıyaslanarak değerlendirildi.

Bulgular: Her iki grupta yaş, vücut kitle indeksi ve infertilite süresi benzerdi (p=0.35, p=0.56, p=0.067). Gruplar arasında açlık glukoz ve insülin düzeyleri, hormon ve androjen profili, antral folikül sayısı, hemoglobin A1c düzeyi (Hba1c), hirsutizm skoru, LH/FSH oranı ve anti-müllerian hormon (AMH) düzeyleri açısından fark bulunmadı. AMH, antral folikül sayısı (AFC), androjen indeksleri ve LH/FSH oranları, altı aylık tedaviden sonra LOD grubunda daha düşüktü (sırasıyla, p=0.011, p<0.001 ve p=0.002). LOD grubunda klinik gebelik ve abortus oranları daha yüksek olmasına rağmen canlı doğum oranları gruplar arasında benzerdi.

Sonuç: Altı aylık tedavi sonunda, her 2 grupta canlı doğum oranları benzer olmasına

ABSTRACT

Introduction:Polycystic ovarian syndrome (PCOS) is a very common ovarian endocrinopathy with a prevalence of 6–21% among women of reproductive age and about 90% among women with anovulatory of infertility . For anovulatory infertility in women with PCOS, laparoscopic ovarian drilling (LOD) has been well-established as a successful second-line treatment for ovulation induction after the failure of clomiphene citrate We aimed to compare laparoscopic ovarian drilling with gonadotropins in terms of efficacy and pregnancy outcomes in second-line therapy of infertile patients with clomiphene citrate resistant polycystic ovary syndrome.

Materials and Methods :A total of 145 clomiphene citrate-resistant volunteer participants with polycystic ovary syndrome were included in the study between June 2017 and December 2019. The patients were divided into two groups; Laparoscopic ovarian drilling was performed in 56 patients, and 89 patients were induction with gonadotropin up to 2 times in a 6-month period. After induction with gonadotropin, ovulation was triggered with recombinant hCG and timed coit was recommended. Patients who underwent laparoscopic ovarian drilling were evaluated at the end of the 6th month. Both groups were compared and evaluated in terms of laboratory parameters and pregnancy results at the end of the 6th month.

Results: Age, body mass index and duration of infertility were similar in both groups (p=0.35, p=0.56, p=0.067). While there was no difference between the groups in terms of fasting glucose and insulin levels, hormone and androgen profile, antral follicle count, level of hemoglobin A1c (Hba1c), hirsutism score, LH/FSH ratio and anti-mullerian hormone (AMH) levels. AMH, antral follicle count (AFC), adrogen indexes and LH / FSH rates were lower in group 1 after six months of treatment (p=0.011, p<0.001, and p=0.002, respectively). Although clinical pregnancy and abortion rates were higher in group 1, live birth rates were similar between groups.

Conclusion: At the end of six months treatment; although live births ratio between groups were similar in clomiphene citrate-resistant PCOS patients, we found that androgen indexes, anti-mullerian hormone, LH/FSH ratio, multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) rate were significantly lower in LOD group so when considering the second-line treatment options of PCOS patients resistant to clomiphene citrate LOD may be more suitable preference.

Keywords: Anti-mullerian hormone; Clomiphene citrate resistance; laparoscopic ovarian drilling; Ovulation induction; polycystic ovary syndrome

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GİRİŞ

Prevalansı 2006 kriterleri ve ESHRE/ASRM 2003 kriterlerine göre %6 ile %21 arasında olan Polikistik Over Sendromu (PCOS), anovulatuar infertilitenin en sık nedenidir (1). PCOS tanısı Rotterdam kriterlerine göre aşağıdaki üç bulgudan ikisini gerektirir: 1) Klinik veya biyokimyasal hiperandrojenizm belirtileri 2) Kronik ovulasyon disfonksiyonu (oligo/ anovülasyon) ve 3) Sekonder nedenlerin dışlanmasından sonra belirgin polikistik over morfolojisi (2).

Gonadotropinler ile ovulasyon indüksiyonu veya laparoskopik ovaryan drilling klomifen sitrata dirençli hastalar için sekonder tedavi seçenekleridir (3). Laparoskopik ovaryan drillingde (LOD) amaç androjen ve luteinize edici hormon (LH) düzeylerini azaltarak ve folikül uyarıcı hormon (FSH) ve seks hormonu bağlayıcı globulini artırarak foliküler gelişimi ve ovulasyonu sağlamaktır. LOD ile metabolik ve androjenik profilin uzun süreli düzelmesine ek olarak, over hiperstimülasyon sendromu (OHSS) riski azalmaktadır (4). İkinci basamak tedavide LOD ile gonadotropinleri karşılaştıran birkaç çalışma varken, meta-analiz iki tedavinin etkinliğini ve komplikasyonlarını karşılaştıran daha ileri çalışmaların gerekli olduğunu ortaya koymuştur (5,6). LOD'nin en büyük avantajı; tekrarlayan tıbbi tedavilere ihtiyaç duymadan devam eden fizyolojik ovulasyon döngüleri sağlar ve potansiyel olarak tekrarlayan gebelikleri sağlamış olur (7).

Ekzojen gonadotropinler ile yüksek gebelik ve canlı doğum oranları elde edilmesine rağmen dezavantajları ; OHSS sıklığı ve çoğul gebelik riskinde artış ile yüksek maliyetler ve yakın takip ihtiyacıdır (8,9).

Klomifen sitrata dirençli PKOS olgularında LOD ve gonadotropinlerin gebelik elde etme üzerindeki etkisini belirlemeyi ve karşılaştırılan parametrelerden hangilerinin canlı doğum oranına olumlu etkisi olduğunu göstermeyi amaçladık.

MATERYAL-METOD

Bu prospektif çalışmaya, PKOS tanısı ile klomifen sitrat tedavisine rağmen en az üç siklus boyunca ovulasyon elde edilemeyen 145 gönüllü hasta dahil edildi. En az 1 yıldır infertilite öyküsü olan ve yaşları 20 ile 35 arasında değişen hastalar çalışmaya alındı. Hastalar rastgele iki gruba ayrıldı; 56 kişiye LOD yapıldı, 89 kişiye gonadotropin verildi.

Gruplar yaş, vücut kitle indeksi (VKİ), infertilite süresi, açlık kan şekeri ve insülin düzeyleri, hemoglobin A1c düzeyi (Hba1c), hirsutizm skoru (Ferriman-Gallwey skoru), antral folikül sayısı (AFC) açısından karşılaştırıldı.

LH/FSH oranı, antral folikül sayısı (AFC), ve AMH seviyeleri siklusun 2. gününde LOD sonrası 3. ayında ve tedavi sonunda 6. ayda değerlendirildi. Gruplar klinik gebelik, abort ve canlı doğum sonuçları açısından da karşılaştırıldı.

Gonadotropin grubunda; rekombinant FSH ile düşük doz step-up protokolü uygulandı. Ardından rekombinant HCG ile trigger yapılıp zamanlı coit önerildi. Ovulasyon indüksiyonu 6 ay içerinde en fazla 2 kez yapılmış olup ,ek tedavi uygulanmamıştır. LOD işleminde ise; 3 mm çapında bir monopolar koter cihazı kullanılarak her 2 overde sekiz delik açıldı. Her bir delik için yaklaşık 5 saniye süren 40 watt enerji kullanıldı. LOD yapılan hastalar herhangi bir ovulasyon indüksiyon ajanı almadan düzenli cinsel ilişki önerilerek 6 ay boyunca takip edildi.

Kan örnekleri 2-8°C'de 15 dakika boyunca 1.000 x g'de santrifüjlendi ve elde edilen serum alikotları daha sonra analize kadar -80°C'de saklandı. Hormon profili için alınan tüm numuneler aynı referans laboratuvarda çalışıldı ve serum AMH seviyeleri Diagnostic Systems Laboratories'den (DSL Inc., Webster, TX, ABD) ticari bir enzim bağlantılı immünosorbent tahlili (ELISA) kiti kullanılarak belirlendi. BMI 30 kg/m2'nin üzerinde olan obez hastaların yanı sıra diyabet, hipotiroidizm, hipertiroidizm veya adrenal hastalık gibi herhangi bir eşlik eden kronik endokrin hastalığı olan hastalar; uterin anomalisi olan ,male faktörü olan hastalar çalışma dışı bırakıldı .

Bu çalışmanın birincil sonucu, gruplar arasında klinik gebelikler, düşükler ve canlı doğum oranlarının karşılaştırılmasıdır. İkincil sonuç, gruplar arasında FSH/LH oranı ve AMH düzeylerinin karşılaştırılmasıdır.Tüm veri analizleri için istatistiksel yazılım Statistical Package for the Social Sciences, sürüm 22.0, SPSS (Inc, New York, ABD) kullanıldı. Niteliksel veriler standart sapmalı ortalamalar ve nicel veriler yüzdelikli sayılar olarak gösterilir. Veri dağılımının normalliği Shapiro- Wilk testi kullanılarak kontrol edildi. Çalışma ve kontrol grupları arasındaki farklılıkların anlamlılığını değerlendirmek için t-testi kullanıldı. Mann-Whitney U testi, bağımlı değişkenler normal dağılmadığında verileri karşılaştırmak için kullanıldı. Korelasyon analizleri Spearman testi kullanılarak yapıldı. İstatistiksel anlamlılığı yansıtmak için p değeri <0,05 olarak kabul edildi.

SONUÇLAR

LOD ile tedavi edilen 56 hastanın ve gonadotropin ile tedavi edilen 89 hastanın demografik, klinik ve endokrinolojik özellikleri Tablo 1'de özetlenmiştir. Gruplar arasında yaş, VKİ, infertilite süresi, bazal hormon profili ve açlık glukoz ve insülin düzeylerini içeren endokrinolojik parametreler, Hba1c düzeyi ve hirsutizm skorları açısından fark istatistiksel olarak anlamlı değildi.

Table 1: Grupların kinik demografik ve endokrinolojik parametreleri

	LOD (n : 56)	**Gonadotropin (n: 89)**	P value
Yaş (yıl)*	28.36±7.24	28.32±7.16	0. 830
BMI (kg/m2)*	27.42±2.48	26.80±2.23	0.780
İnfertilite süresi (yıl)**	3.56±2.34	2.23±1.8	0.067
Açlık Glukoz (mg/dL)*	78.7±9.2	74.9±12.3	0.314
Açlık İnsulin (mU/L)**	4.9 (4.2-5.9)	5.2 (4.8-6.0)	0.256
Tokluk Glukoz (mg/dL)*	94.7±14.9	93.0±17.0	0.430
Tokluk İnsulin (mU/L)**	14.0 (4.5-34.0)	17.4 (9.0- 36.7)	0.186
Hba1c (%)**	5.4 (5.0-6.1)	5.4 (5.0-8.7)	0.333
FSH (D2)(IU/L)*	5.53±0.99	5.68±0.96	0.499
LH (D2) (IU/L)*	10.13±2.12	10.53±1.56	0.642
E_2 (pg/mL)	47.02±19.54	58.84±21.61	0.462
P (ng/mL)	1.84±0.47	1.93±0.24	0.313
PRL (ng/ml)	16.23±8.54	17.67±8.43	0.434
TT(ng/dL)	81.62±5.12	83.24±5.56	0.198
AS (ng/mL)	5.66±1.04	5.50±0.88	0.464
SHBG(nmol/l)	63.85±24.93	61.34±22.34	0.721
Hirsutismus skoru	10 (8-12)	11 (8-14)	0.449
AFC	17.4±3.37	15.3±2.59	0.089
AMH(ng/ml)	10.35±4,49	9.03±3.39	0.208
LH/FSH	1.83±2.14	1.85±1.62	0.980

*Mean±standard deviasyon **median (minimum-maximumLOD: Laparoskopik ovarian drilling; BMI: Body mass index; FSH: Folekül-stimulasyon hormon, LH: Luteinize hormon;E_2: Estradiol P: Progesteron; PRL: Prolaktin TT: Total Testesteron AS:androstenedion, SHBG:Sex hormon-bağlayıcı globulin; AFC: Antral Folekül Count ,AMH: Antimüllerian Hormon

Laparoskopik ovarian drilling sonrası laboratuar ve klinik sonuçlar 3. ay ve 6.ay olarak değerlendirildi. LH seviyeleri, LH/FSH oranı, AMH seviyeleri, total testesteron seviyeleri (TT) ,sex hormon bağlayıcı globülin (SHBG) seviyeleri anlamlı olark düşük tespit edildi , ayrıca antral folikül sayısı LOD grubunda anlamlı derecede düşük tespit edildi.

Tablo 2: Laparoskopik Ovarian Drilling sonrası laboratuar ve klinik sonuçları

	LOD (n = 56)		P value
	3-ay	6-ay	
FSH (IU/L)	5.55±1.22	5.68±1.34	0.511
LH (IU/L)	9.86±2.12	6.53±0.56	**0.023**
LH/FSH	1.77	1.14	**0.045**
TT(ng/dL)	81.72±5.25	73.36±4.68	**0.032**
PRL(ng/ml)	18.62±7.24	16.78±6.86	0.354
E_2 (pg/mL)	58.48±22.6	46.78±18.4	0.086
P (ng/mL)	1.14±0.52	0.94±0.34	0.728
AS (ng/mL)	6.64±1.25	5.26±0.89	**0.041**
AFC	18.4±2.37	14.7±2.29	**0.043**
AMH(ng/ml)	9.56±4,24	8.22±3.33	**0.047**
SHBG(nmol/l)	60.61±23.36	67.73±25.45	**0.040**
Hirsutismus skor	12(9-15)	8(7-11)	**0.032**

*Mean ± standard deviasyon; **n (%) LOD: Laparoskopik ovarian drilling; BMI: Body mass index; FSH: Folekül-stimulasyon hormon, LH: Luteinize hormon; E_2.Estradiol; P: Progesteron;;AS:androstenedion, TT:total testosteron; , SHBG:Sex hormon-bağlayıcı globulin; AFC: Antral Folekül Count ,AMH: Antimüllerian Hormon

LOD tedavisi alan hastaların 6. ayın sonunda gebelik ve komplikasyon sonuçları ile 6 ay içinde en fazla 2 siklus gonadotropinle ovulasyon indüksiyonu yapılan hastaların gebelik ve komplikasyon sonuçları karşılaştırıldı (Tablo 3). OHSS LOD grubunda izlenmedi. ve çoğul gebelik oranları istatistiksel olarak anlamlı derecede yüksek idi..LOD grubunda klinik gebelik oranları gonadotropin grubuna göre daha yüksek tespit edilmesine rağmen ,canlı gebelik oranları açısından gruplar arasında anlamlı fark izlenmedi.

Tablo 3 : Tedavi sonrası gebelik sonuçları

	LOD(n = 56)	Gonadotropin (n = 89)	P value
OHSS**	0(0)	7(7.8)	**0.001**
Çoğul gebelik**	1(4.7)	8(32)	**0.001**
Klinik gebelik**	21(37.5)	28(31.4)	**0.042**
Abort**	6(10.7)	7(7.8)	**0.053**
Canlı Doğum**	15(26.8)	21(23.6)	0.67

*anlamlı çıkan parametreler , aOR, adjusted odds ratio, CI: güven aralığı ; AFC: Antral Folekül Count ,AMH: Antimüllerian Hormon. TT:Total testosteron; , SHBG:Sex hormon-bağlayıcı globulin;

Altıncı ayın sonunda ikili karşılaştırmaları anlamlı bulunan parametrelerin canlı doğum oranları ile ilişkisini ortaya çıkarmak için regresyon analizi yapıldı. AMH, AFC ve SHBG dışında diğer parametreler ile canlı doğum arasındaki korelasyon LOD grubunda istatistiksel olarak anlamlı değildi, (olasılık oranı [OR], 1.86; %95 güven aralığı [GA], 1,324-3,014, OR, 3,07; %95 CI, 1,248-3,245 ve OR, 1,76; sırasıyla %95 CI, 1,146-2,423) ve diğer yandan, gonadotropin grubunda sadece LH/FSH oranı artmış canlı doğum oranları ile ilişkiliydi (OR, 1.65; %95 CI , 1.012–1.364) ve çok değişkenli regresyon analizi sonuçları Tablo 4'te gösterilmektedir.

Tablo 4: Canlı doğum ile ilişkili faktörlerin multivariable analizleri

	LOD grubu			Gonadotropin grubu		
	Aor	95% CI	P value	Aor	95% CI	P value
AMH	1.86	1,324-3,014	0.02*	0.31	0.890-4.470	0.78
AFC	3.07	1,248-3,245	0.03*	0.26	0.841-5.160	0.24
TT	0,67	0,454-1,124	0.26	0.35	0,424-1,014	0.46
LH/FSH	1.14	0.242-0,826	0,34	1.65	1.012–1.364	0.04*
LH	0.36	0.26–3.41	0.86	0.46	0.880–4.083	0.10
SHBG	1.76	1,146-2,423	0.04*	0.86	0.146-1.043	0.39

*anlamlı çıkan parametreler , aOR, adjusted odds ratio, CI: güven aralığı ; AFC: Antral Folekül Count ,AMH: Antimüllerian Hormon. TT:Total testosteron; , SHBG:Sex hormon-bağlayıcı globulin;

TARTIŞMA

LOD ile ovaryan stroma yani ovaryan androjen üretimi tahrip edilir, periferik dokularda androjenlerin östrojene dönüşümü azaltılır. Böylece androjen baskın foliküler ortam östrojen baskın hale gelir.Hormonal ortamın yenilenmesine ek olarak, lokal ve sistemik etkiler ile de foliküler gelişimi ve ovulasyonu iyileştirir (10,11). Ancak overler üzerindeki uzun süreli etkilerinin belirsiz olması, işlem için genel anestezi gerekliliği, yumurtalık rezervi üzerindeki olumsuz etkileri, ameliyat sonrası yapışıklık riski gibi nedenlerle bu yöntemle ilgili bazı endişeler devam etmektedir (12,13). LOD için genel anestezi olmadan artırılmış lokal anestezi altında gerçekleştirilen ofis mikrolaparoskopik over drilling (OMLOD) veya fertiloskopi (transvajinal hidrolaparoskopi) gibi yeni teknikler gündemdedir (14,15).

Klomifen sitrata dirençli polikistik over sendromunda LOD'nin klinik gebeliklerde gonadotropin uygulanan gruba göre gebelik sonuçları üzerinde olumlu etkisi olduğunu gözlemlesek de, klinik gebelik oranı grup 1'de %37.5(21), grup 2'de ise %31.4 (28) (p-değeri =0.042) idi. Gruplar canlı doğum açısından karşılaştırıldığında 6 aylık tedavinin sonunda istatistiksel olarak fark saptanmadı. LOD grubunda abort oranını azaltmak için luteal fazı daha yüksek dozlarda progesteron ile desteklemek gerekti .Çünkü çalışmalar LOD işleminin yumurtalık rezervi üzerinde olumsuz etkilerini göstermiştir (16).Bizde literatür ile benzer şekilde LOD grubunda AMH seviyeleri , SHBG ve LH/FSH oranının düşünün yanısıra ,AF sayısında gonadotropin tedavisine oranla daha fazla düşüş gösterdiğini tespit ettik.

PCOS hastalarında kontrollere kıyasla antral foliküller daha fazla geliştiği ve serum ve foliküler sıvı AMH konsantrasyonları daha yüksek olduğu için foliküler maturasyon kötüdür (17). PCOS'lu kadınlarda artan AMH seviyeleri, yüksek testosteron ve/veya LH konsantrasyonları değişen oosit olgunlaşması ve düşük embriyo kalitesi ile ilişkilidir (18). Mevcut çalışmamızda AMH, AFC ve SHBG dışında diğer parametreler (TT,LH/FSH , LH) ile canlı doğum arasındaki korelasyon LOD grubunda istatistiksel olarak anlamlı değildi.

Amer ve arkadaşları tarafından LOD'nin AMH ve yumurtalık rezervi üzerindeki etkilerini inceleyen bir meta-analizde LOD sonrası serum AMH konsantrasyonunda istatistiksel olarak anlamlı bir düşüş tespit etmişlerdir. Benzer şekilde bizim çalışmamızda da AMH'deki düşüşün LOD sonrası üçüncü ve altıncı aylar arasında anlamlı olduğunu saptadık (19).

Ekzojen gonadotropinler ile yüksek gebelik ve canlı doğum oranlarına rağmen, bu tedavi protokollerinde OHSS de yaygındır, yüksek çoğul gebelik riski mevcuttur(20). Çalışmamızda gruplar arasında benzer canlı doğum oranlarının yanı sıra LOD hasta grubunda çoğul gebelik ve OHSS riskinin anlamlı derecede düşük olduğunu bulduk. Bu nedenle, LOD, gonadotropin ile kıyaslandığında güvenli ve etkili bir alternatif olarak değerlendirilmelidir.

Her iki grubun polikistik overli hastalardan seçilmesi çalışmamızın en büyük avantajı olarak öne çıkıyor.Ancak literatür incelendiğinde yapılan çalışmalarda gebelik komplikasyonlarının (diyabetes mellitus ,gebelikle ilişkili hipertansiyon gibi) LOD ve diğer tıbbi tedavi seçenekleri arasında değerlendirilip ,benzer olduğu bildirilmiştir (21). Gebeliğe bağlı komplikasyonları gruplar arasında karşılaştırmamış olmamız çalışmamız için kısıtlayıcı bir faktördür.

Regresyon analizinden LOD işleminin AMH, AFC'yi düşürerek ve SHBG artırarak canlı doğum ile de pozitif bir ilişkini tespit ettik. Literatür incelendiğinde başka endikasyonlarla laparoskopik cerrahi yapılan hastalarda (tubal cerrahi,endometriozis) cerrahi sırasında aynı anda LOD iyi bir seçim olarak değerlendirilmiştir (22,23) Klomifen sitrata dirençli PKOS hastalarının ikinci basamak tedavi seçenekleri göz önüne alındığında, LOD işlemi bu hastaların danışmanlığında tekrar gözden geçirebilecek faydalı bir tedavi alternatifi olarak düşünülebilinir.

Sonuç olarak, LOD ile tedavi edilen ve ekzojen gonadotropinler ile ovulasyonu indüklenen PKOS hastaları arasında gebelik oranlarının benzer olduğunu, ancak LOD grubunda OHSS ve çoğul gebelik oranlarının daha düşük olduğunu bulduk.

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The effect of oxidative stress on the etiopathogenesis of primary dysmenorrhea

Primer dismenore etiyopatogenezinde oksidatif stresin etkisi

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ÖZ

Amaç: Bu araştırmanın amacı, primer dismenoresi olan hastalarda serum oksidatif stres belirteçleri ve antioksidan enzim düzeylerini karşılaştırarak oksidatif stresin dismenore etyopatogenezine etkisini araştırmaktır.

Yöntemler: Hastanemiz kadın hastalıkları polikliniğine başvuran primer dismenoresi olan 38 kadın ve dismenoresi olmayan 21 kadın çalışmaya dahil edildi. Çalışmaya alınan kadınların her birinden siklusun 3. ve 21. gününde kan örneği alındı. Paraoksonaz (PON), Arilesteraz (ARES) ve Stimulated Paraoksonaz (SPON) serum düzeylerine bakıldı. PON, ARES ve SPON düzeyleri hasta ve kontrol grupları arasında ve her grup içinde siklusun 3. ve 21. gününde karşılaştırıldı.

Bulgular: Çalışmamızda hasta ve kontrol grupları arasında yaş ortalamasında anlamlı fark bulundu. Menarş yaşı, düzenliliği ve süresi açısından anlamlı fark gözlenmedi. Menstrüel siklusun 3. ve 21. günlerinde bakılan ARES, PON ve SPON düzeylerinde hasta ve kontrol grupları arasında anlamlı fark bulunmadı.

Sonuç: Çalışmamızın sonuçlarına göre, hasta ve kontrol grupları arasında siklusun 3. ve 21. günlerinde bu belirteçlerin düzeylerinde anlamlı bir fark bulunmadı. Buna dayanarak, oksidatif ve antioksidan belirteçlerin dismenore etiyopatogenezinde doğrudan yer almadığını veya siklustan bağımsız etki ettiğini düşünmekteyiz.

Anahtar Kelimeler: primer dismenore, oksidatif stres, paraoksonaz, arilesteraz

ABSTRACT

Aim:The aim of this research is to investigate the effect of oxidative stress on the etiopathogenesis of primary dysmenorrhea by comparing serum oxidative stress markers and antioxidant enzyme levels

Methods:A total of 38 women with primary dysmenorrhea and 21 women without dysmenorrhea who applied to our hospital's gynecology clinic were included in the study. Two blood samples were taken from each of the women included in the study, on the 3rd day and the 21st day of their menstrual cycle. The serum levels of Paraoxonase (PON), Arylesterase (ARES), and Stimulated Paraoxonase (SPON) were examined. PON, ARES, and SPON levels were compared between the patient and control groups, as well as within each group, on the 3rd and 21st days of menstrual cycles.

Results: In our study, a significant difference was found in the mean age between the patient and control groups. No significant differences were observed in terms of age at menarche, regularity, and duration. No significant differences were found in the ARES, PON, and SPON levels examined on the 3rd and 21st days of the menstrual cycle between the patient and control groups.

Conclusion:According to the results of our study, there was no significant difference in the levels of these markers between the patient and control groups on their respective menstrual cycle days. Based on this, we believe that oxidative and antioxidant markers are not directly involved in the etiopathogenesis of dysmenorrhea or they exhibit cycle-independent effects.

Keywords: Dysmenorrhea, Oxidative Stress, Paraoxonase, Arylesterase

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INTRODUCTION

Dysmenorrhea is one of the most common causes of pelvic pain in women of all ages and races (1). Results ranging from 45% to 90% have been reported in studies conducted on the prevalence of dysmenorrhea. The variations in results can be attributed to differences in pain perception related to dysmenorrhea, societal differences and the assessment criteria of pain perception (2). Dysmenorrhea is evaluated as primary and secondary. Primary dysmenorrhea refers to menstrual pain that is not associated with organic pathology. According to a study by Rodrigues AC et al., it was reported that 65% of adolescents and young adults had limitations in their daily activities due to dysmenorrhea (3). Studies conducted on female adolescents and young women report the prevalence range of primary dysmenorrhea from 20% to 90% in Turkey (4,5). Although the treatment of dysmenorrhea varies, including conservative treatment, medical treatment, physical therapy and rehabilitation, there is no definitive treatment method that has proven effective for all women (6,7). While the etiopathogenesis of primary dysmenorrhea remains uncertain, studies have shown increased levels of prostaglandins (PGF2α, PGE2) and vasoactive mediators in the endometrium and menstrual blood. The increased levels of PGF2α in the endometrium during the secretory and menstrual phases, specifically, stimulate uterine contractions and reduce uterine blood flow. It is believed that the resulting uterine hypoxia and ischemia contribute to menstrual pain (8,9).

Oxidative stress (OS) occurs as a result of an imbalance between reactive oxygen species and other radicals and antioxidants. The formation of free radicals, which are highly reactive and unstable molecules that can occur in the organism under physiological conditions, and the rate at which they are removed by antioxidant systems are in balance. As long as this balance is maintained, the organism is not affected by free radicals. OS is the disruption of this balance in favor of reactive oxygen species (ROS) (10,11).

It is suggested that oxidative stress plays a role in the etiology of ischemia and hypoxia occurring in dysmenorrhea. Studies focusing on the relationship between dysmenorrhea and oxidative stress have gained prominence in recent years. In a study conducted by Kalia et al., although there were signs of oxidative stress in primary dysmenorrhea, no evidence of oxidative stress-related damage was found in patients (12). In contrast, Kaplan et al. found an association between oxidative stress and primary dysmenorrhea in their study (13).

Our aim in this study is to evaluate the paraoxonase and arylesterase enzyme activities in the different phases of menstruation in primary dysmenorrhea, assess the impact of ROS/antioxidant systems on the etiopathogenesis of dysmenorrhea and contribute to the literature in understanding the etiopathogenesis of primary dysmenorrhea. Knowledge of dysmenorrhea pathophysiology will also contribute to the literature in terms of developing effective treatments.

MATERIALS AND METHOD

Our study was planned as a prospective cohort study. A total of 59 women between the ages of 18-49 were included in our study, consisting of 38 female patients who applied to our hospital's gynecology clinic with primary dysmenorrhea and 21 controls without primary or secondary dysmenorrhea. The criteria used for the diagnosis of primary dysmenorrhea were the onset of dysmenorrhea symptoms within 2 years after menarche, the absence of organic pelvic pathology and the pain starting with menstrual bleeding and ending within 48-72 hours (14). Patients with organic gynecological pathologies (such as fibroids, ovarian cysts, adenomyosis), those who had undergone abdominal surgery, and those using intrauterine devices were excluded from the study in both groups. The participants' age, BMI (body mass index), educational status, parity, age of menstruation onset, duration, and regularity were recorded. The pain during menstruation was assessed using the Visual Analog Scale (VAS) pain scale. The blood samples pf the participants were collected on the 3rd (d3) and 21st (d21) days of their menstrual cycle to evaluate paraoxonase and arylesterase enzyme activities. Our study was approved by the ethics committee of our hospital, with decision number 213, on 24.10.2018.

Collection and Preservation of Blood Samples

Venous blood samples were collected from the participants included in the study after an eight-hour fasting period, and within one hour the collected blood samples were centrifuged at 3200 rpm for 10 minutes in order to separate the serum. Serum samples with hemolysis were not included in the study. The separated serum samples were transferred to sterile tubes and stored at -80°C for preservation to investigate PON1 and Arylesterase levels. At the time of the study, all serum samples were studied in the biochemistry laboratory after they were brought to room temperature.

Measurement of paraoxonase enzyme activity

Paraoxonase activity, which is an antioxidant enzyme with lipophilic and hydrophobic properties associated with HDL cholesterol, was measured using the commercial Rel Assay kit. In this method, the paraoxonase enzyme hydrolyzes the substrate paraoxon (O,O-diethyl-O-p-nitrophenylphosphate), leading to the formation of the coloured product p-nitrophenol. The absorbance of the resulting product was monitored at 412 nanometers (nm) in kinetic mode, and the enzyme activity is expressed as U/L.

Measurement of arylesterase enzyme activity

The arylesterase activity of paraoxonase enzyme was also measured using the commercial Rel Assay kit. This test is based on the colorimetric measurement of phenol, which is generated from the hydrolysis of phenyl acetate substrate by the enzyme in the sample. Due to the high levels of enzyme activity, the results are expressed as kU/L.

Statistical Analysis

Descriptive statistics for continuous data include Mean Standard Deviation, Median, Minimum, and Maximum values, while categorical data was presented in percentages. The conformity of the data to the normal distribution was examined using the Shapiro-Wilk test, and the homogeneity of the variances was examined using the Levene test. The T-test was used for the comparison of data showing normal distribution between the experimental and control groups, while the Mann-Whitney U test was employed for the comparison of data that did not exhibit normal distribution. The Chi-Square test and Fisher's Exact test were used for group comparisons of nominal variables (in cross-tabulations). The Repeated Measures Analysis of Vari-

ance was used to examine the differences between the D3 and D21 values in the two groups for data that demonstrated normal distribution and had homogeneous variances. The Wilcoxon Test was used to compare the separate D3 and D21 values within the groups for data that did not conform to normal distribution or had non-homogeneous variances. The Mann-Whitney U test was employed to compare the two groups. Pearson and Spearman's Correlation Coefficients were utilized to examine the relationships between continuous variables. IBM SPSS Statistics 20 software was used for the evaluations, and the statistical significance threshold was set at $p<0.05$. For the study, support was received from the AYBU BAP office with the project number of 5240/2019.

RESULTS

In our study, the mean age of women in the patient group was found to be 24.26±4.91, while in the control group, it was 27.28±4.89. There was a statistically significant difference in the mean age between the two groups (p=0.027). The median VAS score for menstrual pain in the patient group was 8 (6-10), while in the control group, it was 1 (2-0). There is a difference in the VAS scores for menstrual pain between the two groups (p=0.000). The VAS scores for menstrual pain in the patient group were found to be significantly higher compared to those in the control group. There were no significant differences in BMI, age at menarche, and menstrual duration between the patient and control groups. The data is summarized in Table 1.

Table 1: Comparison of menstrual characteristics of women in patient and control groups

	Patient (n=38)	**Control (n=21)**	***p***
Age (year)	24.26±4.91	27.28±4.89	0.027*
BMI (kg/m²)	22.72±3.67	22.28±2.38	0.620
Menstrual cycle			
Menarche age (year)	12.95±1.31	12.86±1.11	0.683
Duration (day)	5.95±1.69	6.33±1.56	0.362
VAS	8.38±1.38	2.00±0.00	0.000*

(VAS= visual analogue scala)While there were no differences observed between the patient and control groups regarding menstrual cycle regularity and having given birth to children, women in the patient group were found to have a lower educational level compared to women in the control group. The data is summarized in Table 2

Table 2: Demographic data of patients

	Total (n=59)	**Patient (n=38)**	**Control (n=21)**	***P***
Education level (n,%)				
Primary	1 (1.7)	0 (0)	1 (2.6)	
High-school	11 (18.6)	0 (0)	11 (28.9)	
Undergraduate	29 (49.2)	7 (33.3)	22 (57.9)	0.000*
Graduate	18 (30.5)	14 (66.7)	4 (10.5)	
Children (n,%)				
Yes	7 (11.9)	4 (19)	3 (7.9)	0.233
None	52 (88.1)	17 (81)	35 (92.1)	
Cycle regularity (n,%)				
Regular	44 (74.6)	17 (81)	27 (71.1)	0.403
Irregular	15 (25.4)	4 (19)	11 (28.9)	

There were no significant differences found in the ARES, PON, and SPON levels measured on D3 and D21 between the patient and control groups. The data is summarized in Table 3.

Table 3: Comparison of Antioxidant levels of patient and control group on the day3 and day21 of menstruation,

	Patient group (n=38)	**Control group (n=21)**	***P***
3rd day of menstrual cycle (d3)			
ARES	177.47±34.13	175.58±25.86	*0.827*
PON	197.11±126.07	184.82±118.19	*0.862*
SPON	598.87±324.32	563.87±355.87	*0.669*
21st day of menstrual cycle (d21)			
ARES	184.93±41.09	180.39±45.03	*0.697*
PON	185.18±116.41	200.40±128.39	*0.716*
SPON	568.25±309.09	557.23±327.08	*0.776*

No differences were observed in the ARES, PON, and SPON levels based on cycle days within the patient and control groups. The data is summarized in Table 4.

Table 4: Comparison of day3 and day21 Antioxidant Levels in Patient group and Comparison of day3 and day21 Antioxidant Levels in Control Group, (ARES=arylesterase), (PON=paraoxonase), (SPON= Stimulated Paraoxonase)

	Patient			**Control**		
	day 3	**day 21**	***p***	**day 3**	**day 21**	***P***
ARES	177.47±34.13	184.93±41.09	*0.299*	175.58±25.86	180.39±45.03	*0.701*
PON	197.11±126.07	185.18±116.41	*0.925*	184.82±118.19	200.40±128.39	*0.339*
SPON	598.87±324.32	568.25±309.09	*0.766*	563.87±355.87	557.23±327.08	*0.848*

DISCUSSION

Dysmenorrhea is frequently observed in menstrual cycles where ovulation occurs and pelvic pathology is not present. Despite its common occurrence, the etiopathogenesis of dysmenorrhea is not fully understood. Certain experimental and clinical studies suggest that increased levels of uterine prostaglandins can lead to increased myometrial tone and subsequent uterine ischemia, which is proposed as the cause of pain (9,15).

Different results have been reported in studies examining the relationship between the prevalence of primary dysmenorrhea and age. In their study, Kaplan et al. found a decrease in the frequency and severity of primary dysmenorrhea with the advance of age (13). Although the prevalence of primary dysmenorrhea decreases with age, it has been reported to be most common in the ages ranging between 20-24 years (16). However, Harlow et al., in their study, concluded that there is no relationship between dysmenorrhea and age (17). In our study, we found that the mean age of women with primary dysmenorrhea was significantly lower compared to the control group. We also observed that dysmenorrhea complaints decreased as the level of education increased. Considering the socioeconomic impact of dysmenorrhea, the concept of pain and the measurement of its severity become crucial. The Visual Analog Scale (VAS) was used to assess pain in our study, and the average pain intensity according to the VAS was determined as 8.38±1.38. We believe that higher levels of education result in the dismantling of existing and/or constructed taboos surrounding menstruation, as well as an increase in awareness. Studies have shown a decline in dysmenorrhea complaints after childbirth(13,18). Gürel et al. stated that there is no relationship between dysmenorrhea and parity or history of miscarriage (19). In our study, we found no significant difference in childbirth rates between women with and without dysmenorrhea.

Psychological factors and prostaglandins are considered to play a role in the etiopathogenesis of dysmenorrhea. The primary prostaglandins, PGF2 alpha and prostaglandin E (PGE), particularly PGF2 alpha, are believed to induce uterine contractions, decrease blood flow, and lead to uterine hypoxia and ischemia, especially during the luteal and menstrual phases of the endometrial cycle, which is thought to contribute to the development of menstrual pain (8,9). The ischemia and hypoxia occurring in dysmenorrhea suggest the involvement of oxidative stress in its etiology.

Oxidative stress occurs as a result of the imbalance between reactive oxygen species and other radicals and antioxidants. It is a consequence of increased free radical formation and/or decreased physiological activity of antioxidant defenses (20). ROS are continuously generated during normal cellular metabolism and are neutralized by the antioxidant defense system. Oxidative stress occurs when there is an imbalance between the production of ROS and the antioxidant defense system, favoring an increase in ROS production (21). Antioxidant molecules such as PON and arylesterase are part of the defense system against free oxygen radicals that occur in the body.

Paraoxonase has two important functions, which are detoxifying organophosphate compounds like paraoxon and hydrolyzing lipid peroxides to prevent the oxidation of LDL. Studies have demonstrated that paraoxonase (PON1), as one of the endogenous free radical scavenging antioxidant systems in the body, eliminates lipid-soluble carcinogenic radicals formed as a result of lipid peroxidation (22-24). It has been noted that the PON1 enzyme not only hydrolyzes paraoxon but also exhibits similar activities such as arylesterase, lactonase, low-level peroxidase, and phospholipase A2 enzymes (25-28). Paraoxonase is known to demonstrate antioxidant and anti-inflammatory properties through lipopolysaccharide inactivation, and it is believed that PON1 activity is inversely proportional to oxidative stress in both serum and macrophages (29).

Basini et al. evaluated the modulation of ROS production in granulosa cells under hypoxic conditions and demonstrated that, in this case, ROS production decreased, while superoxide dismutase and peroxidase production increased (30). Verit et al. investigated the relationship between the endometriosis stage and PON levels, and a significant association was found in the advanced stages of the disease (31).

In recent years, studies have been conducted to investigate the relationship between dysmenorrhea and oxidative stress. In a study conducted by Kaplan et al. it was found that there was an association between oxidative stress and primary dysmenorrhea. In this study, lipid peroxidation, reduced glutathione, glutathione peroxidase, and total antioxidant values were studied in patients with primary dysmenorrhea and they were found to be significantly higher in healthy controls (13). Similarly, Turhan et al., in their study, found that plasma MDA (malondialdehyde) levels were higher in patients with dysmenorrhea than in those without dysmenorrhea (32). MDA is an enzyme that correlates with the degree of lipid peroxidation, which plays a role in lipid peroxidation. The degree of increase in lipid peroxidation products after oxidation is directly proportional to susceptibility to

oxidation. In a study conducted by Dikensoy et al., they also identified higher plasma levels of MDA, nitric oxide (NO), and adrenomedullin (AM) in patients with primary dysmenorrhea (33).

In our study however, no significant difference was found in PON, ARES, and SPON values between the patient and control groups in samples taken during different phases of the menstrual cycle (D3/D21). In a similar study conducted by Demirdöğen et al. evaluating PON activity in pseudoexfoliative glaucoma based on the role of prostaglandins in the etiopathogenesis, no significant differences were found (34). These results suggest that antioxidant enzymes such as ARES, PON, and SPON may not be effective in hypoxia or ischemia caused by prostaglandin release. Similarly, in a study by Kalia et al., although there were signs of oxidative stress in premenstrual syndrome, no evidence of oxidative stress-related damage was found. They suggested that this could be due to the strong antioxidant properties of not only progesterone but also estrogens, which can exhibit a protective and adaptive response against oxidative stress, supported by previous studies (12). We believe that the similar findings in our study may be attributed to this hormonal effect.

Our study is significant in terms of being the first study to measure the activity of Paraoxonase and Arylesterase enzymes in different phases of the menstrual cycle in patients with primary dysmenorrhea. We examined the balance of oxidative stress and antioxidant systems in the etiopathogenesis of primary dysmenorrhea, specifically focusing on the secretory and luteal phases. However, we did not find any significant results when evaluating these parameters between the patient and control groups and across different phases of the menstrual cycle. Further investigation into the oxidative/antioxidant balance, which is believed to play a role in the etiopathogenesis of primary dysmenorrhea, is necessary to contribute to our understanding of dysmenorrhea etiology. Comprehensive studies that explore other components of the system may be planned to demonstrate the clear relationship between dysmenorrhea and oxidative stress.

Conflict of Interest

We declare that we have no conflict of interest

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Sperm Cryopreservation in Cancer Patients: 13 Years Experience
Kanser Hastalarında Sperm Kriyoprezervasonu: 13 yıllık Tecrübe

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ÖZ

Amaç: 13 yıldır farklı kanser tanılarıyla sperm kriyopreservasyonu yaptığımız hastaların semen parametreleri YUT-ICSI (Yardımcı Üreme Teknolojileri-intrasitoplazmik sperm enjeksiyonu) siklusla rında kullanımı ve mevcut depolanma durumlarının araştırılması.

Gereç ve Yöntemler: Ankara Bilkent Şehir Hastanesi Üremeye Yardımcı Tedavi Merkezine (Kasım 2019-Nisan 2023) ve Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Üremeye Yardımcı Tedavi Merkezine (Ocak 2010- Eylül 2019 arası) başvuran 318 malignite tanısı konulan hastaya fertilitesinin korunması amacıyla sperm kriyoprezervasyonu yapılmıştır. Yaş, kanser türü, semen hacmi, sperm sayısı, sperm hareketliliği, örneklerin saklama ve ART siklusla rında kullanım durumları kaydedilerek analiz edilmiştir.

Bulgular: 13 yılda 318 hastaya sperm dondurma yapıldı. Hastalarda sıklıkla testis kanseri (%54,7), lenfoma (%17,3) ve lösemi (%10,1) görüldü. En yüksek ortanca semen hacmi değeri lösemide (3,1 (1,5-6,0)), en düşük ortanca semen hacmi değeri ise üriner sistem tümöründe (1,5 (1,0-2,0)) izlendi. Ortanca sperm konsantrasyonları testis kanserinde 12,5 (1,0-100,0)x10^6/mL; lenfomada 40,0 (1,0-140,0)x10^6/mL; lösemide 24,5 (1,0-130,0) x10^6/mL'dir. Testis kanserli erkeklerde sperm konsantrasyonunun önemli ölçüde azaldığı görüldü. En yüksek sperm motilitesi nazofaringeal tümör grubunda (40,0 (20,0-60,0)) görüldü. Merkezimizde dört hastaya dondurulmuş spermleri çözdürülerek beş adet YUT (ICSI) siklusu yapıldı. Embriyo transferi dört hastaya uygulandı. Hastalardan birisinde anormal fertilizasyon, bir hastada ise ikiz klinik gebelik saptandı. Üç hasta dondurulmuş spermlerini başka bir merkeze nakletti.

Sonuç: Kanser tedavisinde kullanılan cerrahi yöntemler, kemoterapi ve radyoterapinin, spermatogenez ve fertilite sağlığı üzerinde olumsuz etkilere sahip olmasından dolayı, sperm kriyoprezervasyonu bu hastalarda altın standart olup, kanser hastalarının tedavi öncesi doğurganlık potansiyelinin korunması için pratikte giderek daha fazla önerilmekte ve uygulanmaktadır.

Anahtar Kelimeler: Kriyoprezervasyon, fertilite korunması, sperm kriyoprezervasyonu, testis kanseri, malignite

ABSTRACT

Aim: The study represents 13 years experience of sperm cryopreservation for different cancer types by researching the semen parameters, the use of frozen-stored samples in ART-ICSI (Assisted Reproductive Technologies-intracytoplasmic sperm injection) cycles, and their current storage status.

Material and Methods: Sperm cryopreservation in order to fertility preservation was conducted on 318 patients who had different malignancies applied to the Reproductive Center of Ankara Bilkent City Hospital (from November 2019 to April 2023) and Zekai Tahir Burak Women's Health Hospital (from January 2010 to September 2019). The age, cancer type, semen volume, sperm count, sperm motility, samples storage status, and usage of banked sperm in ART cycles were recorded and analyzed.

Results: Sperm cryopreservation was applied to a total of 318 patients for 13 years. The major cancer types are testicular cancer (54.7%), lymphoma (17.3%), and leukemia (10.1%). 11% (n=35) of patients. The highest median semen volume was detected in leukemia (3.1 (1.5-6.0)), and the lowest mean semen volume was in the urinary system tumor (1.5 (1.0-2.0)). The median sperm concentration in testicular cancer is 12.5 (1.0-100.0)×10^6/mL; in lymphoma is 40.0 (1.0-140.0)×10^6/mL and in leukemia is 24.5 (1.0-130.0)×10^6/mL. Sperm concentration significantly decreased in men with testicular cancer. The highest median of sperm motility was observed in nasopharyngeal tumor group (40.0 (20.0-60.0)). Four patients applied to our center to use their frozen sperm. The patients underwent five ART (ICSI) cycles and four embryo transfers. One of the patients had abnormal fertilization and one of the patients had twin clinical pregnancy. Three patients transferred their banked sperm to another center.

Conclusion: Since surgical methods, chemotherapy and radiotherapy treatments used for cancer treatment have intense negative effects on spermatogenesis and fertility health, sperm cryopreservation is the gold standard and increasingly being recommended in clinical practice for preserving the fertility potential of cancer patients before treatment.

Keywords: Cryopreservation, fertility preservation, sperm cryopreservation, testicular cancer malignancy

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INTRODUCTION

Cancer is a general health problem seen worldwide. In the 1980s, the primary objective for both patients and physicians was survival. However, thanks to advancements in surgical techniques, chemotherapy, and radiotherapy, coupled with improved early diagnosis, the odds of curing and prolonging the lives of patients have markedly improved. The survival rate especially in lymphoma and testicular cancers has reached over 90% (1). Accordingly, the phenomenon of reproduction, which is associated with the quality of life, has come to the fore. The increased awareness of both patients and their relatives as well as physicians has led to increase importance of sperm cryopreservation in the last 10 years over all the world (2). Sperm cryopreservation is the most precious and effective method to preserve fertility potential in cancer patients (3). Efforts to fight against fertility impair the mental health of couples, so sperm freezing has great importance in couples to reduce stress about infertility (4). Recent technological developments, and innovations in freezing techniques and media, led to close values of motility and morphology similar to normal patients in thawing sperms, as well as making it safe to refer (5). Surgical methods, chemotherapy, and radiotherapy treatments effect on spermatogenesis by damaging germinal tubule epithelium caused oligozoospermia or azoospermia and also disrupt neural signals regulating the erection and the ejaculation (6). Dose and frequency of treatment can be determined for fertility health, but it cannot be clearly predicted in which patient's spermatogenesis will be impaired in a what proportion (7). For this reason, sperm cryopreservation is recommended especially before treatment for all patients who are single or married want to have children. Unfortunately, the use of frozen sperm in cancer patients is very low in Turkey.

We represent our 13 years of experience in the study by determining cancer types, patient ages, semen parameters (volume, concentration, motility), and the use and storage status of sperm samples who applied to our fertility center.

MATERIAL AND METHODS

1. Subject and study design

Sperm cryopreservation was conducted on a total of 318 patients who applied to the Department of Gynecological Endocrinology and Reproductive Medicine of Ankara Bilkent City Hospital (from November 2019 to April 2023) and Zekai Tahir Burak Women's Health Hospital (from Janbuary 2010 to September were collected retrospectively. Patients who have azoospermia or insufficient motile spermatozoa in semen samples were not frozen and not included in to study. Data of patients included the following: age, diagnosis, day of sexual abstinence, semen volume, sperm count and motility, current banking status and also usage of the frozen spern ART cycles.

2. Ethics statement and legal procedure

The study protocol was approved by the Ethical Committee of Ankara Bilkent City Hospital (E2-23-4587). To be sperm frozen legally in our country, there must be a report signed by three physicians stating the diagnosis of patient and recommendation of sperm cryopreservation. Sperm cryopreservation consent form was informed and signed by patients. The information form was signed by the parents in patients under the age of 18.

Frozen sperm samples are legally stored for one year in our country. After one year, the patient's confirmation for storage or annihilation needs to be taken at the end of each subsequent year. Also, patients have option to use their sperm samples in our fertility center or have the option of moving to another center for ART cycles. If the patient dies, all samples are destroyed after the death report is obtained.

3. Sperm preparation and cryopreservation

Patients were advised to come with 3-5 days of sexual abstinence. Sperm cryopreservation was admitted immediately, regardless of sexual abstinence in patients with urgency to prevent disruption of treatment. Semen samples were collected in sterile plastic containers through masturbation in our center. Samples were allowed to liquefy for 30-45 minutes at 37C. After liquefaction, a drop of semen sample was taken to Makler counting chamber. Concentration and percentage of motile spermatozoa were determined according to World Health Organization guidelines (8). The semen samples were transferred into a conical bottom tube (BD Bioscience, San Jose, CA, USA) and diluted 1:1 with sperm rinse solution (Vitrolife, Gothenburg, Sweden) and then centrifugated two times. After the supernatant was discarded, 0.2–0.5 ml of sperm rinse medium was added to sperm pellet and mixed with the same volume of sperm freezing medium (Vitrolife, Gothenburg, Sweden), and the mixture was taken to High Security cotton-plugged sperm straws (Cryo Bio System, L'Aigle, France). The prepared straws were kept in nitrogen vapor for 30 minutes and then storaged in liquid nitrogen tanks (-196°C).

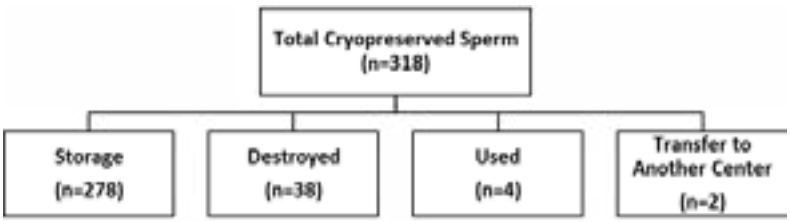
Corp.) and MS-Excel 2007 programs were used for statistical analyzes and calculations. Statistical significance level is accepted as $p<0.05$. The suitability of the continuous variables to normal distribution was evaluated graphically and with the Shapiro-Wilks test. It was determined that none of the continuous variables followed a normal distribution. Mean±SD (standard deviation) and Median (Minimum-Maximum) values were given to display the descriptive statistics of the variables. Kruskal Wallis non-parametric analysis of variance was used to compare the parameters. Bonferroni correction was made for pairwise comparisons.

RESULTS

Characteristics of patients

Sperm cryopreservation has been made in this center since 2010. Figure 1 represents study chart. There was a total of 318 men had cryopreservation due to different malignancies. A total of 38 sperm samples were legally destroyed until now. Some of them were due to destruction requests of the patients, death of the patient, and some of them were due to the fact that the patients could not be reached for years or the patient did not come to the sperm extension procedure for extension of storage. Sperm samples of three patients were transferred to another center in 13-years period. Also, Five ICSI cycles were performed in four patients by using thawed sperms. The remaining sperm straws of one of the four patients who underwent ICSI are waiting to be destroyed due to patient death, one patient transferred his samples to another center, and the remaining straws of two patients are still stored after thawing.

Figure 1. Flow chart of the study



The types of cancers were presented in Table 1. Of men (n=318) who underwent sperm cryopreservation; 54.7% (n=174) had testicular cancer, 17.3% (n=55) had lymphoma, 10.1% (n=32) had leukemia, and 6.6% (n=21) had soft tissue tumor, 3.5% (n=11) had osteosarcoma, 3.8% (n=12) had gastroenterological tumor, 1.9% (n=6) had nasopharyngeal tumor, 1.2% (n=4) had brain tumor, 0.9 % (n=3) had urinary system tumor. The highest number of indications for sperm cryopreservation were in testicular cancer. Lymphoma and then leukemia followed testicular cancer, respectively. The lowest diagnosis was observed in urinary tumor.

Table 1. Cancer type of patients before sperm cryopreservation

Cancer type	No. of patient (%)
Testicular cancer	174 (54.7)
Lymphoma	55 (17.3)
Leukemia	32 (10.1)
Nasopharyngeal tumor	6 (1.9)
Soft tissue sarcoma	21 (6.6)
Brain tumor	4 (1.2)
Osteosarcoma	11 (3.5)
Urinary system tumor	3 (0.9)
Gastroenterological tumor	12 (3.8)

Age at cryopreservation and sexual abstinence of patients are shown in Table 2. The lowest sperm cryopreservation age was 14 years old in four patients. 11% (n=35) of all patients (n=318) are adolescents under the age of 18. The mean age of men with testicular cancer is 26.26±5.67, with lymphoma is 25.20±7.03, with leukemia is 26.47±7.13, with nasopharynx tumor is 20.17±6.05, with soft tissue sarcoma is 24.19±6.90, with brain tumor is 22.00±5.89, with osteosarcoma is 22.73±8.01, with urinary system

tumor is 25.00±11.79, with gastroenterological tumor is 33.83±7.99 years old. The highest average age was observed in the gastroenterological tumor group and the lowest age group was observed in the nasopharynx group. A significant difference was detected between the mean age at sperm cryopreservation between nasopharynx tumors (20.17±6.05) and gastroenterological tumors (33.09±7.93) (=21.251, p=0.007).

Table 2. Semen characteristics and details of patients according to cancer type.

Diagnosis	Age at Cryopreservation (year)	Sexual Abstinence (day)	Semen Volume (mL)	Sperm Concentration (X106)	Sperm Motility (a+b motil)
	M±SD Median	M±SD Median	M±SD Median	M±SD Median	M±SD Median
Testicular cancer	26.26±5.67	5.80±7.61	3.32±1.34	18.66±18.70	31.72±16.49
	25.0 (16.0-45.0)	4.0 (1.0-67.0)	3.0 (0.4-10.0)	12.5 (1.0-100.0)	30.0 (3.0-70.0)
Lymphoma	25.20±7.03	7.00±9.10	2.73±1.13	44.13±33.08	29.84±14.86
	24.0 (14.0-41.0)	4.0 (1.0-60.0)	2.8 (0.2-5.5)	40.0 (1.0-140.0)	30.0 (2.0-70.0)
Leukemia	26.47±7.13	8.09±5.46	3.44±1.24	29.91±26.31	21.97±14.84
	26.0 (14.0-42.0)	7.0 (1.0-25.0)	3.1 (1.5-6.0)	24.5 (1.0-130.0)	20.0 (2.0-55.0)
Nasopharyngeal tumor	20.17±6.05	3.17±2.04	3.22±0.93	63.33±46.44	41.17±14.70
	17.5 (16.0-32.0)	3.0 (1.0-7.0)	3.1 (2.0-4.5)	60.0 (11.0-124.0)	40.0 (20.0-60.0)
Soft tissue sarcoma	24.19±6.90	5.76±6.26	2.89±1.31	44.86±34.65	30.33±13.27
	23.0 (14.0-40.0)	4.0 (1.0-30.0)	2.8 (0.7-6.0)	40.0 (1.0-120.0)	30.0 (7.0-55.0)
Brain tumor	22.00±5.89	5.75±1.50	2.12±1.18	23.50±12.04	26.00±6.98
	22.0 (16.0-28.0)	6.0 (4.0-7.0)	2.3 (0.5-3.3)	21.0 (12.0-40.0)	25.5 (18.0-35.0)
Osteosarcoma	22.73±8.01	6.54±2.21	2.57±0.99	44.18±37.83	30.64±15.76
	24.0 (14.0-38.0)	7.0 (3.0-10.0)	3.0 (1.0-4.0)	32.0 (4.0-120.0)	30.0 (5.0-60.0)
Urinary system tumor	25.00±11.79	11.33±16.17	1.50±0.50	35.33±40.46	23.00±27.73
	22.0 (15.0-38.0)	2.0 (2.0-30.0)	1.5 (1.0-2.0)	14.0 (10.0-82.0)	8.0 (6.0-55.0)
Gastroenterological tumor	33.83±7.99	6.67±7.76	2.91±1.76	34.17±29.53	30.83±16.35
	36.0 (18.0-43.0)	4.5 (2.0-30.0)	2.7 (0.7-6.0)	29.0 (2.0-100.0)	35.0 (10.0-60.0)
	=23.546; p=0.003	=21.560; p=0.006	=21.561; p=0.006	=47.561; p<0.001	=13.185; p=0.106

Sperm parameters

Semen parameters (volume, concentration, motility) of patients are shown in Table 2. Even if the duration of sexual abstinence was preferred to be between 3-5 days, sperm freezing was performed regardless of the duration of sexual abstinence, in patients who had emergency to be done chemotherapy and radiotherapy. The highest median (min-max) sexual abstinence was detected in leukemia (7.0 (1.0-25.0)) and osteosarcoma (7.0 (3.0-10.0)). Statistically significant difference was found between testicular cancer and leukemia in terms of sexual abstinence (p<0.05).

The highest median (min-max) semen volume was detected in leukemia (3.1 (1.5-6.0)), and the lowest mean semen volume was in the urinary system tumor (1.5 (1.0-2.0)). In the pairwise comparison of malignancies in terms of semen volumes, a statistically significant difference was detected between urinary system tumor and testicular cancer, urinary system tumor and leukemia, lymphoma and testicular cancer (p <0.05).

The lowest sperm concentration median (min-max) was observed in patients with testicular tumor (12.5 (1.0-100.0), followed by urinary system tumor (14.0 (10.0-82.0)), brain tumor (21.0 (12.0-40.0), leukemia (24.5 (1.0-130.0), gastroenterological tumor (29.0 (2.0-100.0)), osteosarcoma (32.0 (4.0-120.0)), soft tissue sarcoma (40.0 (1.0-120.0), lymphoma (40.0 (1.0-140.0)), nasopharyngeal tumor 60.0 (11.0-124.0), respectively. It was observed that sperm concentration was not prominently affected by lymphoma (40.0 (1.0-140.0)). In the pairwise comparison of the groups in terms of sperm concentrations, statistically significant differences were found between lymphoma and testicular cancer and also between soft tissue tumor and testicular cancer (=48.623, p<0.001), (Table 2).

The highest median (min-max) of sperm motility was observed in the nasopharyngeal tumor group (40.0 (20.0-60.0)). Leukemia (20.0 (2.0-55.0)) and urinary system tumors (8.0 (6.0-55.0)) showed lower sperm motility than other cancers (Table 2). But no statistically significant difference was detected in terms of sperm motility (in the rate of progressive motile spermatozoa (a+b)) (p>0.05).

The outcome of ICSI cycles made with thawed sperms

Reproductive outcomes of thawed sperms are represented in Table 3. Four patients (one of them is lymphoma, one of them is osteosarcoma, and two of them are testicular cancers) applied to thawing sperm in their ART cycles. A total of five ICSI cycles were performed to patients. Twin clinical pregnancy occurred in one of the patients, had two embryo transfer, made in the second ICSI cycle. The pregnant patient was the wife of patient with testicular cancer. Unfortunately, the pregnancy ended at the 18th week. No live birth was observed. Abnormal fertilization was observed in another patient. Embryo transfer was cancelled. Pregnancy results were negative in the other two patients.

DISCUSSION

The ability to successfully freezing and storing reproductive cells and thawing them has great importance for the development of ART. Cryopreservation has not only increased the success of ART cycles, but also contributed to the preservation of fertility health before testicular surgery, chemotherapy and radiotherapy (7). Depending on the type and dose of the agent used in chemotherapy and radiotherapy, spermatogenesis may be permanently, temporarily, or long-term damaged and cause sperm DNA damage (7). Spermatogonia is highly affected due to their intense mitotic activity from radiotherapy. Spermatids are very sensitive to therapeutic agents because they do not have DNA repair ability (9). Especially in patients used high doses of alkylating and cytostatic agents' azoospermia may become (10). Before treatments, spermatogenesis can be disrupted, oligospermia can be seen in 60% of patients because of testicular tumors, leukemia, and lymphoma. When chemotherapy or radiotherapy is given to these patients in this condition, spermatogenesis can sometimes be damaged in a way that can only return to normal in 4-5 years or disrupted permanently (1,3,11). In this case, it is important to inform the patient and determine the type of treatment. Sperm cryopreservation in a such patient is gold standard for preserving fertility health in the future. The American Society of Reproductive Medicine Ethics Committee (12) and the American Society of Clinical Oncology (13) both recommended that physicians should inform all cancer patients about the option for fertility preservation. Experts recommended sperm freezing before gonadotoxic treatments to protect sperm from DNA damage caused by therapeutic agents and ensure to freeze with better sperm parameters. Although it is an undesirable situation, the patient may apply for sperm freezing in the middle or after the treatment (14). Although sperm freezing is frequently performed, the rate of use sperm thawing by cancer patients is low through assisted reproductive techniques and varies between 10% and 60% (14), 3% and 10% (15) in worldwide. One of the reasons why sperm banks are rarely used in cancer patients is that some patients can regain spermatogenesis after treatments and natural conception has been reported to be 23–47% in these cases (16). Pregnancy rates achieved with frozen sperm vary between 12% and 35.2% (17).

The general principle in gamete cryopreservation is cooling the material after equilibrating with cryoprotectants, and then storing it in liquid nitrogen at -196°C. After this process, gonad cells have been stored for decades (18). If sperm storage conditions are optimal, storage time does not have a negative impact on sperm quality. Conducted studies has demonstrated relationship between post-thawing sperm parameters and the duration of storage time (19). During thawing process, the cryoprotectants are removed from the samples and transferred back into physiological environments where maintain their vitality (18). Cryoprotectant agents reduce the freezing point while replacing water, reduces the solute and salt ratio of the cell, and protect the cells from high osmolarity and provide controlled water loss. The main purpose of these procedures is to return the sperm cells with as little damage as possible when thawed.

Different methods in freezing and thawing mediums are currently being developed to protect sperm against the negative effects of freezing and thawing process' (18, 20).

Song et al., (1) conducted a study at 21 years of sperm cryopreservation, examined the diagnosis and sperm parameters of 721 cancer patients, and found that the sperm count in patients with testicular cancer was significantly lower than others, similar to our study. This may be caused by freezing after unilateral orchiectomy in patients with testicular cancer. They detected that 44 patient (6.1%) used their stored sperm via ART cycles. 22 clinical pregnancy was confirmed by ultrasound. In another study, conducted by Vomstein and colleagues (21) in 545 patients who had different cancers, showed that the lowest sperm values were in testicular tumors, in parallel to our study, 29 (5.3%) patients used their banked sperm in 48 ART cycles, and 15 clinical pregnancies were achieved. Fu et al., (22) showed that sperm parameters were negatively affected by testicular tumor and leukemia in 145 patients who underwent sperm cryopreservation (from 2006 to 2017). They conducted ART cycles to 9.7% (n=14) of patients returned to use for banked sperm and a total of 33 ART cycles were performed. Pregnancy occurred in 51.5% (17 out of 33 cycles) of patients. 71.4% of patients had a baby (10 out of 14).

In the present study, a total of 318 men performed to sperm cryopreservation had different malignancies. In parallel with previous studies (1, 21,22), the lowest sperm concentrations were observed in patients with testicular tumor. Although the most common group of patients who underwent sperm cryopreservation was testicular cancer followed by lymphoma, sperm parameters were found to be less affected than other cancers in lymphoma. Leukemia is the third common malignancy sperm cryopreserved and the second malignancy negatively affected in terms of sperm concentration. No statistically significant difference was detected in terms of progressive motility among all cancer types. The lowest sperm cryopreservation age was 14 years old in four patients who had leukemia, lymphoma, osteosarcoma, and soft tissue tumor. The storage period in the sperm bank depends on the patient's survival, patient's marriage status, recovery of spermatogenesis and the patient's application to continue storing of the samples. The longest duration time of stored sperm is 13 years in our center. In 13 years, 38 sperm samples were destroyed because of the patient died, had a spontaneous child, applied for destruction, or the patient could not be reached for a long time. Three patients' samples were transferred to another center upon application of the patients. The use of cryopreserved sperm due to oncological malignancy is very low in our center. Only four patients (1,25%) applied to use frozen sperms to have a baby. Five ICSI cycles were made with thawed sperm. Embryo transfer was made in four patients. Abnormal fertilization occurred in a patient and embryo transfer was canceled. Twin clinical pregnancy occurred in a patient's second cycle. Unfortunately, the babies were lost in the 18th pregnancy week. There was no live birth. The limitation of this study is that since the number of patients who applied to the ART cycle with frozen sperm is very small, it needs to be conducted for a longer period of time and with a larger number of patients in order to determine the effects of cancer type and semen values on ART outcomes.

According to these data, we emphasize that the use of frozen sperm should be encouraged. Sperm cryopreservation is a significant hope and it is worth to use for the patient before gonadotoxic treatments.

CONCLUSION

Since surgical methods, chemotherapy and radiotherapy treatments used for cancer treatment have intense negative effects on spermatogenesis and fertility health, Sperm cryopreservation is the gold standard and increasingly being recommended in clinical practice for preserving the fertility potential of cancer patients before treatment especially in testicular cancer and leukemia. Thanks to the developing assisted reproductive techniques today, sperm cryopreservation is done more safely and successfully to preserve fertilization patients diagnosed with cancer before chemotherapy or radiotherapy that will affect spermatogenesis.

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CHANGES IN THE ANXIETY LEVELS OF PREGNANT WOMEN IN THE SECOND YEAR OF THE COVID-19 PANDEMIC

COVID-19 PANDEMİSİNİN İKİNCİ YILINDA GEBELERİN KAYGI DÜZEYİNDEKİ DEĞİŞİKLİKLER

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ÖZ

Amaç: COVID-19 pandemisinin başlangıcından bu yana son iki yılda gebelerin kaygı düzeylerindeki değişimi incelemek ve sosyodemografik özelliklerin bu düzeyleri nasıl etkilediğini belirlemek

Method: Antenatal polikliniğine pandemi sürecinde iki yıl arayla başvuran 200'er düşük riskli gebeye gebelik haftalarından bağımsız Durumluk-Sürekli Kaygı Envanteri uygulandı. Gebelerin sosyodemografik özellikleri not edildi. Sonuçlar iki yılın sonunda değerlendirildi.

Bulgular : Gebelik haftası, çalışma durumu, gebeliğin planlanıp planlanmadığı ve eş desteği istatistiksel olarak iki grup arasından anlamlı bir fark oluşturmadı (p|>0,001). Gebelerin pandemi başlangıcındaki durumluk ve sürekli kaygı ortalamaları, iki yıllık dönemden sonraki gebelere göre daha yüksekti (sırasıyla, p=0,000,p=0,038). Pandemi başlangıcında gebe olanlarda yaşa bağlı anksiyete düzeylerinde bir fark bulunmazken, iki yıl sonraki periodda gebelikte anne yaşı arttıkça sürekli kaygı düzeyinin arttığı belirlendi (p=0,047). Primigravidlerin anksiyete düzeyi multiparlara göre daha yüksek bulundu. Pandemi nedeniyle sosyal kısıtlamalar uygulanırken çalışan gebelerin kaygı düzeyleri çalışmayanlara göre daha düşüktü (p=0,049).

Sonuç: Sosyal kısıtlamalar sırasında çalışmak, hastalık bulaşması nedeniyle oldukça riskli görünse de, sosyal destek gebelerde kaygı düzeyinin azaltılmasında olumlu etkiye sahiptir. Bu nedenle büyük afetlerde kullanılabilecek gebelere yönelik psiko-sosyal destek programları hazırda tutulmalıdır.

Anahtar Kelimeler: Kaygı, Gebelik, Covid 19 pandemisi

ABSTRACT

Objective: To examine the changes in the anxiety levels of pregnant women in the last two years, since the onset of the COVID-19 pandemic and to determine how sociodemographic characteristics have affected these levels.

Study Design: State-Trait Anxiety Inventory (STAI) was given to 400 low-risk pregnant women visiting the antenatal outpatient clinic within a two-years interval regardless of their gestational age. Besides the anxiety inventory, the sociodemographic characteristics of the participants were also noted.The results were evaluated at the end of two years.

Results: Gestational week, working status, whether the pregnancy was planned or not, and partner support were not statistically significant between groups(p|>0.001). The averages of state and trait anxiety of pregnant women were higher at the beginning of the pandemic than the pregnant women were after two years period(p=0,000,p=0,038, respectively). While there was no difference related to age at the beginning of the pandemic, the level of trait anxiety increased as the mother's age increased in the period after two years(p=0.047). The anxiety level of primigravids was found to be higher compared to the multipars. Pregnant women who were working while the social restrictions were being imposed due to the pandemic had lower anxiety levels than those who were not(p=0.049).

Conclusion:Even though working during social restrictions seems quite risky because of the disease transmission, it has a positive effect on reducing the level of anxiety in pregnant women with social support. Therefore, psycho-social support programs for pregnant women should be kept ready in major disasters.

Keywords: Anxiety, Covid-19 pandemic, pregnancy

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INTRODUCTION

The coronavirus outbreak, which was declared a pandemic by the World Health Organization in March 2020, has affected the entire world and caused many financial and intangible losses (1). While unknowns are still playing a key role in this disease, which started in China and has affected the whole world, studies on treatment methods and vaccines's complications are still continuing. As of March 2022, 6.2 million people worldwide had died (2). It remains unknown who is more likely to be infected and who is less, what determines the course of the disease, and whether there is a cure or not, and vaccination is still an issue. In the early days of the pandemic, many countries limited movement into and out of the country imposed social restrictions, and even imposed lockdowns(3).

During this period, issues such as the course of the disease in pregnant women and fetuses, whether there is vertical transmission from the mother to the baby, and how often pregnancy follow-ups should be performed have caused concern all over the world. Previous pandemic reports indicated that the pregnant population was more sensitive than healthy people who were not pregnant(4). Along with social restrictions, the difficulties associated with pregnant women being able to come to their routine follow-ups have made the already sensitive gestation period even more difficult. In the intervening two years, information about the disease has increased, new prevention methods have been added to the existent ones, and social restrictions have been removed, thanks to mass vaccination. In this study, we investigated whether there was a difference in the anxiety levels of the pregnant population during and after the devastating impact of the pandemic and the factors affecting this. Thus, we tried to answer the question of how to support pregnant women psycho-socially in a similar event that may occur in the future.

MATERIALS AND METHOD

The study was carried out in the obstetrics department of a tertiary hospital in Ankara, which is classified as a reference hospital during the pandemic. After the approval of the ethics committee (E1-20-708) for the study, the State-Trait anxiety inventory was delivered to 200 low-risk pregnant women who came to the antenatal outpatient clinic at the beginning of the pandemic in March 2020. The first 10 patients who applied to the antenatal outpatient clinic and were accepted to fill the inventory were chosen for 20 consecutive workdays as the study group. The same procedure was performed in March 2022 which was accepted as a date when the restrictions due to the pandemic loosened. The high-risk pregnant women (multiple pregnancies, intrauterine growth retardation, fetal anomalies, presence of preterm birth risk, gestational hypertension, gestational diabetes), pregnant women with known additional diseases or known psychiatric illnesses, and patients with COVİD -19 infection were excluded from the study. The results were evaluated by a single researcher at the end of two years.

State-Trait Anxiety Inventory:

This inventory was developed by Spielberg and his colleagues to measure the level of state and trait anxiety and has been widely used since then(5). The inventory includes two separate scales consisting of a total of 40 items. The state anxiety inventory is a measurement tool that indicates how the person feels at a given moment, while the trait anxiety inventory is a measurement tool that indicates how the person usually feels. The emotions or behaviors expressed in the items of the state anxiety scale are measured using the following options aiming to evaluate the severity of the experience: 1) Not at all, 2) Somewhat, 3) Moderately so, and 4) Very much so. The emotions or behaviors expressed in the Trait Anxiety Inventory items are measured using the following options which aim to find out the frequency of the emotion or the behavior: 1) Almost never, 2) Sometimes, 3) Most of the time, and 4) Almost always. The two inventories are filled one after another, and scores are obtained. The total score from both of the scales ranges from 20 to 80. A large score indicates a high level of anxiety whereas a small one indicates a low level of anxiety (6).

Statistical Analysis:

400 subjects were conducted in the study. The collected data were transferred to IBM SPSS Statistics 23. When evaluating the study data, we considered frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables. We used an independent sample t-test to determine whether there was a difference between the two groups, and one-way variance analysis (One Way ANOVA) to determine whether there was a difference between more than two groups. As a result of the one-way variance analysis (ANOVA), we used the Levene test to examine the variance homogeneity, and the multiple comparison test (Bonferroni or Tamhane's T2) to identify which group or groups caused the difference. We used Bonferroni to examine the difference between groups in variables that provided variance homogeneity, and Tamhane's T2 test to examine the difference between groups in variables that did not provide variance homogeneity. We did a Chi-square analysis in the examination of the relationship between categorical variables and a Pearson correlation analysis in the examination of the relationship between measurements. We accepted $p<0.05$ for the significance level.

RESULTS

While there was no statistically significant difference between the groups in terms of work status, gestational week, planned pregnancy status, and partner support ($p>0.05$), there was a statistically significant difference between the age, educational status, and gravidity status between the groups ($p<0.05$). The average age of pregnant women at the beginning of the pandemic was higher ($p=0.047$). While the rate of high school graduates was high in pregnant women at the beginning of the pandemic, the proportion of university graduates is higher in pregnant women after two years period($p=0.00$). In addition, the number of women who have had more than three pregnancies is higher at the beginning of the pandemic (Table-1).

Table 1. Examining the relationship between groups and demographic characteristics (N=400)

	At the beginning of the pandemic	At the end of the pandemic	Total	Test/p				
	N	%	N	%	N	%		
Age (mean.±sd)	28,50±5,33a	27,47±4,93b	27,98±5,15	1,996/0,047*1				
Education status	Primary school	21	10,5	12	6,0	33	8,3	19,657/0,000*2
	Middle school	48	24,0	42	21,0	90	22,5	
	High school	101	50,5a	79	39,5b	180	45,0	
	University	30	15,0b	67	33,5a	97	24,3	
Work status	Working	53	26,5	70	35,0	123	30,8	3,393/0,0652
	Not working	147	73,5	130	65,0	277	69,3	
Gravidity	1	88	44,0	87	43,5	175	43,8	8,060/0,045*2
	2	60	30,0	77	38,5	137	34,3	
	3	42	21,0a	23	11,5b	65	16,3	
	4	10	5,0	13	6,5	23	5,8	
Gestational week (mean. ±sd)	23,88±8,40	22,84±10,58	23,36±9,56	1,094/0,2751				
Planned pregnancy status	Planned	140	70,0	157	78,5	297	74,3	3,779/0,0522
	Unplanned	60	30,0	43	21,5	103	25,8	
Partner support	Present	200	100,0	198	99,0	398	99,5	2,010/0,4992
	Absent	0	0,0	2	1,0	2	0,5	

a, b: shows the differences between the average/percentage of groups (a=highest mean/percentage).

1: Independent sample t-test, 2: Chi-square test, *:p<0.05

There was a statistically significant difference between the groups in terms of state anxiety and trait anxiety levels (p<0.05). The averages of state anxiety and trait anxiety levels of pregnant women at the beginning of the pandemic were higher than currently pregnant women(Table 2).

Table 2. Examination of differences between groups in terms of anxiety status (N=200)

	At the beginning of the pandemic (mean.±sd)	At the end of the pandemic (mean.±sd)	Total (mean.±sd)	Test/p
State anxiety	39,23±8,72	35,10±8,35	37,16±8,78	4,830/0,000*1
Trait anxiety	43,26±7,20	41,73±7,52	42,49±7,39	2,078/0,038*1

1: Independent sample t-test, *:p<0.05

There is a positive significant correlation between the levels of state and trait anxiety in pregnant women in both groups (p<0.05) (Table-3).

	At the beginning of the pandemic	At the end of the pandemic	
	Trait anxiety	Trait anxiety	
State anxiety	R	0,318	0,568
	P	0,000*	0,000*

r: Pearson correlation coefficient, *:p<0.05

As shown in Table 4 , while there was no statistically significant difference in the levels of state anxiety between educational status, work status, and planned pregnancy status in pregnant women at the beginning of the pandemic (p>0.05), there was a statistically significant difference between their gravidity status (p<0.05). The average state anxiety level in pregnant women at the beginning of the pandemic with two pregnancies was higher than in those with one pregnancy.

Table 4. Examining the relationship between measurements and demographic characteristics in groups (N=400)

	State anxiety	Trait anxiety			
	At the beginning of the pandemic (mean.±sd)	At the end of the pandemic (mean.±sd)	At the beginning of the pandemic (mean.±sd)	At the end of the pandemic (mean.±sd)	
Education status	Primary school	43,14±7,69	36,83±8,35	44,57±6,49	44,67±5,40
	Middle school	40,04±9,02	35,10±8,06	44,94±6,92	42,07±7,39
	High school	38,60±8,68	35,10±8,30	42,92±7,54	41,27±7,76
	University	37,27±8,49	34,79±8,74	40,77±6,33	41,52±7,66
Test/p2	2,270/0,082	0,200/0,896	2,427/0,067	0,753/0,522	
Work status	Working	37,55±9,37	35,13±9,33	41,58±6,88b	41,09±7,59
	Not working	39,83±8,43	35,08±7,82	43,86±7,24a	42,07±7,49
Test/p1	-1,640/0,103	0,034/0,973	-1,985/0,049*	-0,881/0,379	
Gravidity	1	37,11±9,15b	34,33±7,84	42,33±6,88	40,54±7,09
	2	40,80±7,53a	34,74±8,84	44,67±6,79	41,97±8,31
	3	40,33±8,41	36,43±8,63	42,76±7,92	42,91±6,30
	4	43,70±9,59	40,00±7,08	45,00±8,62	46,08±5,85
Test/p2	3,611/0,014*	2,009/0,114	1,528/0,209	2,441/0,066	
Planned pregnancy status	Planned	38,47±8,74	35,05±8,30	43,31±7,19	41,53±7,34
	Unplanned	40,98±8,49	35,28±8,63	43,13±7,28	42,44±8,19
Test/p1	-1,878/0,062	-0,158/0,874	0,156/0,876	-0,704/0,482	

a,b: shows the differences between the mean/percentage of groups (a=highest mean/percentage).

1: Independent sample t-test, 2: One-way ANOVA test, *:p<0.05

There was no statistically significant difference in state anxiety status between educational status, study status, gravidity, and planned pregnancy status in pregnant women after two-years period(p>0.05).

While there was no statistically significant difference in the educational status, gravidity, and planned pregnancy status in pregnant women at the beginning of the pandemic in terms of trait anxiety levels, there was a statistically significant difference between the working status (p<0.05). The average trait anxiety measurement of the non-working pregnant women at the beginning of the pandemic was higher than that of working women.

Table 5 shows there was a positive significant correlation between age and state anxiety levels in pregnant women after two years period of the pandemic (p<0.05).

There was no statistically significant difference in state anxiety status between educational status, study status, gravidity, and planned pregnancy status in pregnant women after two-years period(p>0.05).

While there was no statistically significant difference in the educational status, gravidity, and planned pregnancy status in pregnant women at the beginning of the pandemic in terms of trait anxiety levels, there was a statistically significant difference between the working status (p<0.05). The average trait anxiety measurement of the non-working pregnant women at the beginning of the pandemic was higher than that of working women.

Table 5 shows there was a positive significant correlation between age and state anxiety levels in pregnant women after two years period of the pandemic (p<0.05).

Table 5. Examining the relationship between anxiety status in groups (N=200)

	Pregnant women at the beginning of the pandemic	Currently pregnant women			
	Age	Gestational week	Age	Gestational week	
State anxiety	R	0,096	0,100	0,211	0,022
	P	0,178	0,160	0,003*	0,755
Trait anxiety	R	0,045	-0,014	0,089	0,011
	P	0,527	0,847	0,209	0,874

r: Pearson correlation coefficient, *:p<0.05

DİSCUSSION

In this study we compared the data of 200 pregnant women who were admitted to the hospital while social restrictions were continued, there were no vaccines against the virus, and the efforts to understand the pregnancy-disease relationship were challenged by the presence of only a limited number of cases, and the data of 200 other pregnant women two years after the pandemic started, when they admitted for their regular follow-ups after the restrictions were removed, vaccination became widespread, and information regarding the disease began to increase. When we compared the anxiety levels of the pregnant women at the beginning of the pandemic and those of pregnant women after two years, we determined that the rate of planned pregnancies have increased. At the beginning of the pandemic, the ratio of planned pregnancy was 70%, while it was 78.5% after two years . We observed that pregnant women who were able to admit to the hospital for routine control at the beginning of the pandemic were predominantly high school graduates (50.5%), while pregnant women were predominantly university graduates after the restrictions were removed. (39.5%) At the beginning of the pandemic,the trait anxiety levels of primigravidas were not different compared to those with a second pregnancy, but they had a higher level of state anxiety. This finding was mentioned in another study conducted at the beginning of the pandemic in our country, which stated the fact that the anxiety levels of those who had their first pregnancy were higher than multipars(7). A study that Lebel et al. conducted in Canada during the pandemic reported higher levels of anxiety in primiparous (8). Another study found that first-time pregnant women may have relatively high anxiety levels because of concerns about the baby's health status, physical changes experienced by pregnant women, and fear of childbirth(9).

In previous studies, it was established that the pandemic has a significant effect on the mental health of pregnant women and that perinatal anxiety is significantly higher than it was in the pre-pandemic period(10, 11). In this study,the averages of state and trait anxiety levels of pregnant women were found to be higher at the beginning of the pandemic in social restrictions. In a prior study conducted in our country, similar results were found when restrictions were removed but there was no vaccination (7). Therefore, the widespread use of the vaccine resulted with a significant decrease in the anxiety levels of pregnant women.

In a retrospective study, Zhou et al. reported that advanced age and chronic diseases posed a significant risk of death from COVID-19. This was later supported in some meta-analyses (12, 13). In our study, we found no significant difference in age-related anxiety scores in pregnant women at the beginning of the pandemic, but the anxiety score increased as the age increased in pregnant women after two years period. This situation may be related to the increase in insights into the relationship between the disease and age.

While we expected higher anxiety scores of pregnant women who had to work during social restrictions due to the fear of contagion at the beginning of the pandemic, we did not find a significant difference in state anxiety scores.However, contrary to expectations, the trait anxiety scores of those who did not work were significantly higher than those who worked. This may be attributed to the fact that better social support reduces anxiety symptoms, as stated in the literature(7, 14). This social support includes the pregnant woman's family, social environment, and medical staff. It has been made clear in our study that not only medical diagnoses and treatment should be provided for pregnant women, but also adequate psychosocial care should be taken, and support should be given by pregnant woman's family, social environment and health professionals during such pandemics.

CONCLUSION

Studies conducted during the COVID-19 pandemic have clearly reported that the pandemic has had a significant impact on the mental health of pregnant women. Stress-related pregnancy complications are an important cause of morbidity and mortality for both mothers and newborns. These complications can be reduced with the protective effect of psychosocial support. Therefore, psycho-social support programs for pregnant women should be kept ready in major disasters.

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Olgu Sunumu / Case Report

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A Fatal Neonatal Case of CHARGE Syndrome and Mini-Review of the Literature

Fatal Seyirli Bir Neonatal CHARGE Sendromu Ogusu ve Kısa Literatür Taraması

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ÖZ

Bu makalede, yenidoğan döneminde ölümcül seyreden bir CHARGE sendromu vakası sunulmuştur ve kısa bir literatür taraması yapılmıştır. Böylece CHARGE sendromlu bireylerin yaşamlarının erken dönemlerinde karşılaştıkları konjenital anomalilerin ve klinik semptomların çok çeşitli oluşunun altı çizilmek istenmiştir. Karakteristik dismorfik yüz özellikleri, konjenital kalp hastalığı ve şiddetli beslenme intoleransı ile bu hasta, sendromun çok sayıda organ-sistemi etkileyerek ne kadar karmaşık olabileceğinin ve tanı almayan çok hafif fenotipte olgular bulunmakla birlikte, ciddi erken ölümcül vakalarla da sonuçlanabileceğinin iyi bir örneğidir.

Anahtar Sözcükler: CHARGE sendromu, yenidoğan, fenotipik değişkenlik, genetik tanı

ABSTRACT

In this article, we present a neonatal fatal case of CHARGE syndrome and provide a mini-review of the literature to underline the wide range of congenital abnormalities and clinical symptoms that individuals with CHARGE syndrome face early in life. This patient, with his characteristic dysmorphic features, congenital heart defects, and severe feeding intolerance, is a good example showing the complexity of the syndrome. CHARGE syndrome might affect numerous organ systems and result in severe early lethal cases for some whereas some of the cases show a very mild phenotypic spectrum and may go unrecognized.

Keywords: CHARGE syndrome, newborn, phenotypic variability, genetic testing

INTRODUCTION

CHARGE syndrome, a multiple malformation syndrome, is a rare genetic syndrome with an estimated incidence of 1/8,500-15,000 live births (1, 2). The inheritance is autosomal dominant, and most cases result from de novo mutations. Although the name CHARGE is an acronym representing coloboma, congenital heart defects, choanal atresia, retardation of growth, developmental delay, genital abnormalities, ear abnormalities, and deafness, it is a complex syndrome with a broad phenotype that can involve almost all organ-systems including extremity, vertebra and kidney abnormalities, omphalocele and umbilical hernia, brain and cranial nerves alterations, cochlear dysplasia, cleft lip and palate, thymus/parathyroid abnormalities, tracheoesophageal fistula, and autism spec¬trum disorder. The complexity of the syndrome makes it challenging for clinicians to provide accurate and comprehensive care. There is also a striking variability in severity with both very mild cases and severe early lethal cases.

CASE REPORT

A male infant was transferred to our neonatal intensive care unit right after the delivery at 39 gestational weeks via C/S because of respiratory distress and an antenatal diagnosis of cleft lip and palate and hypoplastic left heart. He was the second child of non-consanguineous healthy parents. On physical examination, he was an appropriate-for-gestational-age infant, and he had dysmorphic features composed of cleft lip and palate, low set dysplastic ears with lack of lobes, short

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webbed neck, microphthalmia, and coloboma of the left eye. He was intubated, and mechanical ventilation was started. Transthoracic echocardiography revealed hypoplastic left heart with complete atrioventricular septal defect (complete AVSD). Cranial ultrasound (US) was normal, and the abdominal US uncovered dilated aperistaltic intestinal segments consistent with ileus so the enteral feeding had held up until the first meconium discharge was seen. Ophthalmologic examination detected wide chorioretinal coloboma in the left eye.

He remained in critical condition during hospital admission retaining any surgery for correction of the congenital defects. The multitude of issues he faced further complicated the management besides the major heart defect. He was administered broad-spectrum antibiotic treatment, inotropic agents, calcium and thyroid hormone replacement treatment, oral decongestive therapy with furosemide and captopril for late neonatal sepsis, septic shock, hypocalcemia, hypothyroidism, and congestive heart failure. Enteral feeding issues were another challenge to overcome. It took too long to reach full enteral feeding at about 38th day of life because of intermittent abdominal distention and enteral feeding intolerance periods. Extubation was tried many times but failed. Unfortunately he died on the 43rd day of life with the official cause of death identified as congenital heart defect.

Table1. Prevalance of common features in CHARGE syndrome based on three recent cohorts with moleculary confirmed CHARGE patients.

	Zentner et al. (2010)	Bergman et al. (2011)	Legendre et al. (2017)
Coloboma	190/253 (75%)	189/234 (81%)	67/92 (73%)
Heart malformations	193/250 (77%)	191/252 (76%)	58/92 (63%)
Choanal atresia	95/247 (38%)	99/179 (55%)	38/89 (43%)
Retarded growth	101/141 (72%)	35/94 (37%)	
Developmental delay	107/141 (76%)	147/149 (99%)	
Inner ear abnormalities	98%	110/117 (94%)	87/88 (99%)
External ear malformations	214/235 (91%)	224/233 (97%)	78/91 (86%)
Facial nerve palsy	72/187 (39%)	80/121 (66%)	
Cleft lip and/or cleft palate	79/242 (33%)	79/163 (48%)	18/91 (20%)
Tracheoesophageal anomaly	35/185 (19%)	42/146 (29%)	20/84 (%24)
Genital anomalies	61%	118/145 (81%)	43/77 (56%)
Renal anomalies			25/80 (31%)
Craniaı nerve dysfunction		173/174 (99%)	64/87 (74%)
Feeding difficulties		90/110 (82%)	

Genetic analysis revealed a heterogeneous variant mutation in the CHD7 gene (c.2959C>T p.(R987*) p.Arg987*). Genetic screening for 22q11.2 deletion was negative.

DISCUSSION

The diagnosis of CHARGE syndrome is based on clinical findings criteria that continue to be refined. The most commonly used clinical criteria were described by Blake, Verloes, and Hale in 1998, 2005, and 2016, respectively (3-5). All three sets of criteria make a distinction between major and minor characteristics and slightly differ from each other in the number of characteristics that must be present. The major diagnostic criteria include ocular coloboma, choanal atresia, specific ear anomalies, cranial nerves involvement, and pathogenic CHD7 gene variant. Minor diagnostic criteria include genital anomalies, developmental delay, congenital heart defects, growth deficiency, orofacial cleft, tracheoesophageal fistula, and minor facial anomalies such as a square face with broad prominent forehead, a prominent nasal bridge and a flat columella and midface. Establishment of a clinical diagnosis requires a pathogenic CHD7 variant plus one other major characteristic. If CHD7 testing is absent or the result is negative, then at least three major or two major and three minor characteristics are sufficient for diagnosis.

Our patient fits the diagnostic criteria for CHARGE syndrome with his cleft lip and palate, characteristic external ear anomaly (a highly valuable diagnostic clue), microphthalmia, coloboma, heart malformation, feeding difficulties and pathogenic CHD7 variant mutation. CHD7, encoding the chromodomain helicase DNA binding protein, is the only gene currently known to be associated with CHARGE syndrome. The gene is located on region q12 of chromosome 8 and is crucial for the mitigation of neural crest cells affecting a wide variety of tis¬sues. Studies have shown that CHARGE syndrome patients exhibit defects in neural crest migration (6, 7).

To date, several reviews document the frequency of the major features. Table 1 shows the prevalence of specific anomalies found in the CHARGE syndrome population, on the basis of three recent cohorts of molecularly confirmed CHARGE patients from Zentner et al., 2010, Bergman et al., 2011, Legendre et al., 2017 (8-10).

Gastrointestinal tract problems such as gastroesophageal reflux disease, aspiration, and swallowing dysfunction are common in children with CHARGE syndrome and are primarily the result of anatomical malformations that interfere with feeding and cranial nerve IX/X abnormalities affecting gut motility. Our patient's anatomic malformation and ongoing mechanical ventilation necessitated O/G tube feeding. He also showed vagal nerve disfunction from the first day of life documented with abdominal US findings consistent with dysmotility and severe enteral feeding intolerance. Long-term and complex feeding issues can contribute to morbidity and mortality. Feeding difficulties are highly prevalent, often begin at birth and can persist throughout the entire lifespan (11).

The spectrum of congenital heart disease is highly variable in CHARGE syndrome as every type of cardiac defect (except heterotaxy and cardiomyopathy) has been documented. These defects encompass mild cardiac malformations to more severe malformations that require cardiothoracic surgery. As seen in our patient, conotruncal defects and atrioventricular septal defects are relatively over represented (12).

CHARGE syndrome patients can have features that overlap with DiGeorge like hypocalcemia and varying degrees of immune deficiency (13). Our patient suffered from hypocalcemia and severe sepsis that may be a result of underlying immunodeficiency and thymus dysfunction although not documented. FISH analysis for 22q11 deletion was negative.

Neonates with CHARGE syndrome often have multiple life-threatening medical conditions. Poor life expectancy correlated with combinations of major cardiovascular malformations, bilateral choanal atresia, esophageal atresia, severe T-cell deficiencies, and central nervous system anomalies. Feeding difficulties were also found to be a major cause of morbidity at all ages (1, 9, 14-16). Our patient had two major risk factors for poor prognosis, which were the congenital heart anomaly and feeding difficulties, and unfortunately he died on the 43rd day of life.

Optimal management of individuals with CHARGE syndrome should ideally take place in a tertiary center that can undertake all areas of specialist treatment and management, but details of the management are beyond the scope of this article. In 2017 Trider et al., published a comprehensive checklist for the follow up of CHARGE syndrome patients.(17). Our patient is a good example showing the complexity of this syndrome that can affect numerous organ-systems and result in severe early lethal cases, whereas some of the cases show a very mild phenotypic spectrum and may go unrecognized.

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Olgu Sunumu / Case Report

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Geç Foliküler Fazda Rastgele Başlangıçlı Ovaryan Stimülasyon

Random Start Ovarian Stimulation in the Late Follicular Phase

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ÖZ

Genellikle in vitro fertilizasyon (IVF) tedavisinde; kontrollü ovaryan hiperstimülasyona menstrüasyonun 2-3. günü başlanmaktadır. Ancak zamanı kısıtlı olan hasta gruplarında, over hiperstimülasyonu için menstrüasyonun beklenmesi artık yerini "random start protokollere" bırakmıştır. Bu olgu sunumunda, aynı hastanın farklı menstrüel sikluslarda gerçekleştirilen erken ve geç foliküler fazda yapılan ovaryan stimülasyon yanıtları karşılaştırılmıştır.

Anahtar kelimeler: random start ; kontrollü ovaryan stimulasyon

ABSTRACT

Usually in in vitro fertilization (IVF) treatment; controlled ovarian hyperstimulation is started on the 2-3rd day of menstruation. However, in patient groups with limited time, waiting for menstruation for ovarian hyperstimulation has now been replaced by 'random start protocols'. In this case report, the ovarian stimulation responses of the same patient in the early and late follicular phases in different menstrual cycles were compared.

Keywords: Random start; controlled ovarian stimulation ;fertility prezervation

GİRİŞ

Gonadotropinlerle kontrollu ovarian stimulasyon in vitro fertilizasyon tedavisinin önemli bir parçasıdır. Amaç, başarıyı mümkün olan en güvenli şekilde en üst düzeye çıkarmak ve yeterli sayıda oosit elde etmek için folikülleri uyarmaktır. Ancak optimal protokol üzerinde belirsizlikler vardır (1). Daha önce tüp bebek tedavisi görmüş kadınlarda klinik protokol seçimi çok daha kolay görünmektedir. Bir önceki siklusun performansı iyiyse, klinisyenin aynı protokole uyması muhtemeldir. Aksine, önceki siklusun istenmeyen bir sonucu varsa, protokolün değiştirilmesi olasıdır. Sonraki IVF tedavisinde gonadotropin başlangıç dozunun doğru şekilde kişiselleştirilmesi son derece önemli bir klinik karardır.

Tüp bebekte tedavinin bireyselleştirilmesinin temel amacı, her kadına kendine özgü özelliklerine göre en iyi tedaviyi sunmak, böylece başarıyı en üst düzeye çıkarmak , OHSS gibi iyatrojenik riskleri ortadan kaldırmak ve siklus iptali riskini en aza indirmektir. Ayrıca anneliğini kişisel veya profesyonel nedenlerle ertelemek isteyen veya yaşa bağlı doğurganlık düşüşüne karşı korunmak isteyen kadınlar tarafından tercih edilen oosit kriyoprezervasyonu için oosit verimini maksimize etmeyi amaçlayan ovarian stimulasyon protokollerinin optimizasyonu da son derece önemlidir (2).

Geleneksel olarak, GnRH antagonisti ile oosit stimulasyonu foliküler fazın başlangıcında başlatılır. Bu stimülasyon protokolü adet siklusunun geç luteal fazında tek bir antral folikül dalgasının varlığına dayanır. Fakat yapılan çalışmalarda tek bir interovulatuar periyod içinde birden fazla folikül seçim dalgasının olduğu gösterilmiştir. Menstrüel siklusta 2-3 dalga teorisinin gündeme gelmesiyle menstrüel siklusun herhangi bir döneminde stimulasyon tedavisine başlanabilmektedir (3-4). Bu şekilde uygulanan random start oosit stimulasyonu tedavilerinde IVF döngüsü için toplam süre azalarak önemli bir avantaj sağlanır ve acil durumlarda, oosit verimi ve olgunluğundan ödün vermeden rastgele bir siklus tarihinde tedaviye başlanılabilir (5).

Random start ovaryan stimülasyon protokolleri ile oositlerin/embriyoların dondurularak saklanması ile ilgili kanserli kadınlarda çok sayıda çalışma yapılmış olmasına rağmen, elektif koşullarda yapılan kadınlar ile ilgili yeterli sayıda çalışma bulunmamaktadır. Bu olgu sunumunda, hastanın erken foliküler faz ve geç foliküler fazda gonadotropinler ile yapılan ovaryen stimulasyonlarının yanıtları karşılaştırıldı ve literatür eşliğinde değerlendirildi.

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OLGU SUNUMU

39 yaşında 2 yıldır çocuk sahibi olamayan hasta kliniğimize başvurdu. Yapılan ofis histeroskopi doğal olarak izlendi. Hastanın bazal FSH değeri: 8,5 IU/L AMH: 3. 58 NG/ML TSH:2. 5 IU/L olarak izlendi. Yapılan ultrasonografide sağ overde 9-10 sol overde 6-7 antral folikul izlendi. Hastanın eşinin spermiyogram sonucu normal idi.Vücut kitle indeksi 20 olan hastaya ovulatuar bozukluk ve ileri yaş nedeniyle siklusunun 3. gününde antagonist protokol ile 150 IU rekombinant FSH (Gonal-F®) injeksiyonu tedavisi başlandı. İndüksiyonun 5. gününde yapılan ultrasonografide endometrium 8.5 mm sağ overde 15 mm, 14 mm ve 12 mm çaplı 3 adet folikül izlenmesi üzerine tedaviye GNRH antagonisti (Cetrotide®) eklendi. 8. gününde 17 mm boyutunda üç folikul saptandı. Hastaya rekombinant hcg (Ovitrelle®) 250 mcg 1x1 subkutan uygulanarak ovulasyon sağlandıktan 36 saat sonra transvajinal oocyte pick-up (OPU) ile 5 oosit toplandı ve bunlara 3 saat sonra hastanın eşinin spermi ile intrastoplazmik sperm enjeksiyonu (ICSI) işlemi uygulandı. 2 embriyo G1 dönemine kadar gelişti ve 3. gün hastanın onayı ile 2 embriyo transferi yapıldı. Transferden 12 gün sonra kanda yapılan beta-hcg testi negatif geldi. Bir sonraki siklusta geç folikuler fazda başvuran hastaya yapılan ultrasonografide sağ overde 5-6 antral folikül ile 10 mm ve 11 mm boyutunda 2 adet hemorajik kist ve sol overde 7-8 adet antral folikül izlendi.Siklusunun 7. gününde random start protokolu ile 225 IU human menapozal gonadotropin (hMG) (Menopur®) injeksiyon tedavisi başlandı. İndüksiyonun 2. gününden itibaren hastaya GNRH antagonisti (Cetrotide®) injeksiyonu günlük olarak yapıldı. Tedavinin 7. gününde yapılan ultrasonografide endometrium 13 mm ve sol overde 17 mm üzerinde dört folikül saptanınca hastaya rekombinant hcg (Ovitrelle®) 250 mcg 1x1 subkutan injeksiyonu uygulandı. 36 saat sonra gerçekleşen oosit toplama işleminde 10 oosit metafaz II (M2) aşamasında toplandı. 7 tanesi matür olan oositlere 3 saat sonra ICSI işlemi uygulandı. Toplam 4 embriyo blastokist evresine kadar gelişti ve 5nci güne ulaşan 4 blastokist (5AA ve 4BB) donduruldu. 3 ay sonra hastaya 2 adet dondurulmuş embriyo transferi yapıldı. Transferden 12 gün sonra kanda yapılan beta-hcg testi sonucu 1609 mIU/ml geldi. Kontrol beta-hcg değeri 7131 mIU/ml gelen hasta 2 hafta sonra ultrason kontrolü için çağırıldı. Ultrasonda dikoryonik diamniyotik ikiz gebelik izlendi. Her iki fetüsün de kalp atışı görüldü.

TARTIŞMA

Bu olgu sunumunda erken foliküler fazda başlanan ovarian stimulasyon protokulünde 3 matür oosit toplanmasına rağmen geç foliküler fazda random start protokolü ile 7 matür oosit elde edilmiştir. Bu durum random start oosit stimulasyonunun oosit verimi ve olgunluğundan ödün vermeden rastgele bir siklus tarihinde başlayabileceğini destekler niteliktedir.

2014 yılında yapılan bir çalışmada 22 adet random start protokolu 44 adet de standart ovarian stimulasyon protokolu başlanan hasta retrospektif olarak incelenmiş ve random start protokolu uygulanan grupta toplanan toplam ve matür oosit sayısı daha yüksek bulunmuştur (6).

2017 yılında Pereira ve arkadaşlarının yaptığı bir başka çalışmada ise 1302 oosit stimulasyonu yapılan hasta incelenmiştir. Bu hastalardan 859una standart oosit stimulasyonu 443üne ise random start protokolü uygulanmış ve çalışma sonucunda, menstrüel siklusun herhangi bir aşamasında başlatılan random start protokollerinden elde edilen toplam ve MII oosit sayısının, standart oosit stimulasyonu sonuçları ile benzer olduğu ortaya konulmuştur (7).

Von Wolff ve arkadaşları foliküler ve luteal faz sırasında oosit stimülasyonunun sonuçlarıyla ilgili karşılaştırmalı bir çalışma bildirmiştir. Bu çalışmada 28 hastaya foliküler fazda stimülasyon, 12 hastaya luteal fazda GnRH antagonistleri ve rekombinant FSH ile stimülasyon uygulanmıştır. Luteal faz grubu ve foliküler faz grubunda, stimülasyon süresi, toplam gonadotropin dozu,toplanan ve matür oosit sayısında benzer sonuçlar görülmüştür (8).

SONUÇ

Sonuç olarak, bir sonraki menstrüasyonun başlamasını beklemeye gerek kalmadan, menstrüel siklusunun herhangi bir gününde rastgele başlanılan antagonist protokollerinin kullanımı, malign hastalıklar veya diğer tıbbi durumlar için oosit elde etmenin acil olduğu durumlarda günümüzde tercih edilen bir prosedür haline gelmiştir.

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Mikrobiyotanın Yenidoğan Özelinde İncelenmesi ve Yenidoğan Mikrobiyotasını Etkileyen Faktörler

Examination of Microbiota Specific to Newborns and Factors Affecting Newborn Microbiota

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ÖZ

Mikrobiyotanın insan sağlığı, gelişimi, fizyolojisi ve bağışıklığı üzerinde son derece önemli bir etkiye sahip olduğu yapılan çalışmalarda belirlenmiştir. Bunun yanında, mikrobiyota gelişiminin önemine dair günümüzde yapılan artan sayıdaki çalışmalar, bu konu üzerinde önemle durulması gerektiğini ortaya koymaktadır. Sağlıklı bir annenin mikrobiyotasının yenidoğanda sağlıklı mikrobiyotanın temelini oluşturduğu bilinmekte, yaşamın ilk yıllarında oluşan mikrobiyota yapısı, ileriki yıllarda insanların mikrobiyota yapısı, yaşamı ve sağlığı adına birçok açıdan önem taşımaktadır. Bu nedenle, mikrobiyota konusundaki güncel bilgilerin takip edilmesi, yenidoğanın sağlıklı mikrobiyotaya sahip olması ve buna etki eden olumsuz faktörlerin önlenmesine yönelik çaba sarf edilmesi, kadınlara prenatal dönemden itibaren sağlıklı mikrobiyota oluşumuna yönelik destek verilmesi sağlıklı nesillerin oluşması için oldukça gereklidir. Bu nedenle yenidoğan mikrobiyotası ve mikrobiyotayı etkileyen faktörlerin belirlenmesi, literatüre konu ile ilgili derleme niteliğinde kaynak oluşturulması önem arz etmektedir.

Anahtar Kelimeler: Anne, Doğum, Mikrobiyota, Sağlık, Yenidoğan.

ABSTRACT

It has been determined in studies that the microbiota has an extremely important effect on human health, development, physiology and immunity. In addition, the increasing number of studies on the importance of microbiota development reveals that this issue should be emphasized. It is known that the microbiota of a healthy mother forms the basis of the healthy microbiota in the newborn. For this reason, following up-to-date information on microbiota, making efforts to ensure that the newborn has a healthy microbiota and preventing the negative factors affecting it, and providing support to women for the formation of healthy microbiota from the prenatal period are essential for the formation of healthy generations. For this reason, it is important to determine the newborn microbiota and the factors affecting the microbiota, and to create a compilation resource in the literature on the subject.

Keywords: Mother, Birth, Microbiota, Health, Newborn.

GİRİŞ

İnsan vücudunun tüm anatomik boşluklarında yaşayan mikroorganizmaların (bakteri, virüs, arkea ve mantarlar dahil olmak) tümüne "mikrobiyota" denilmektedir (1,2). Mikrobiyota, "insan vücudunun deri, kulak, vajina, ağız gibi çeşitli bölgelerinde yaşayan, solunum sistemi, ürogenital sistem ve sindirim sistemi başta olmak üzere birçok yaşamsal sistemi etkileyen, vücutta ommensal, simbiyotik ve patojenik olarak bulunan mikroorganizmaların tamamı" olarak da tanımlanmaktadır (3). Mikrobiyota ile ilgili yapılan çalışmalarla birlikte yenidoğan mikrobiyotasının başlama zamanı konusunda doğumdan sonra oluşmaya başladığı sonucu hakimken, son yıllarda yapılan çok sayıda çalışmada mikrobiyotanın rahim içinde oluşmaya başladığı kanıtlarına ulaşılmıştır (4,5). Bunlarla birlikte yapılan çok sayıda çalışma neticesinde, mikrobiyota ile ilgili elde edilen kanıtlar artmıştır. Artan bu yeni bilgiler ışığında, yenidoğanın, göbek bağı, plasenta, amniyon sıvı ve mekonyumunda bakterilerle birlikte var olan bir mikrobiyota oluşumu tespit edilmiştir. Ayrıca mikrobiyotanın intrauterin dönemden itibaren oluşmaya başladığı, yetişkinlik döneminde çeşitlilik ve sayı olarak en üst seviyeye ulaştığı, yaşlılığa kadar yaşam boyunca değiştiği ve mikrobiyota popülasyonunun yaşlılık döneminde tekrar azalmaya başladığı elde edilen güncel bilgiler arasındadır (3,5,6).

Her insanın mikrobiyota yapısının farklı olmasında çeşitli faktörler rol almaktadır. Ancak gebeliğin ilk gününden erişkinliğe kadar birçok sistemi etkileyen mikrobiyota üzerinde en belirleyici role sahip faktörün "anne faktörü" olduğu gösterilmiştir. Yenidoğanda mikrobiyota gelişimini etkileyen faktörler literatürde çoğunlukla; "gebelik süresi, vajinal mikrobiyota ve doğum şekli,

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yenidoğanın beslenme şekli, yenidoğanın anne sütü alma durumu, maternal ağırlık kazanımı ve obezite, maternal ilaç (antibiyotik, probiyotik vb.) kullanımı" olarak yer almaktadır (7,8). Bunun yanında yenidoğan mikrobiyotasının "annenin bağışıklık durumu, adet döngüsü, hormonal faktörler, çevresel maruziyet, doğumdan sonra hastanede kalış süresi, cilt bakımı ve kimyasallar, hijyen koşulları, sigara ve alkol kullanımı, stres, cerrahi operasyon geçirme durumu, ekonomik durum, fiziksel aktivite durumu, etnik köken, cinsel aktivite" gibi faktörlerden etkilendiği de belirtilmektedir (9,10).

Yapılan araştırmalarda "mikrobiyota" adı verilen bu mikroorganizma topluluklarının insan sağlığı üzerinde tahmin edilenden daha fazla etkiye sahip olduğu, insanların direncini artırarak dokuları patojenlerden koruduğu, insan sağlığı için önemli olan birçok koruyucu ve metabolik fonksiyon görevini üstlendiği gösterilmiştir (7). Ayrıca günümüzde diyabet, obezite, astım, alerjik hastalıklar, gastrointestinal sistem hastalıkları ve ateroskleroz gibi birçok hastalığın mikrobiyota ile ilişkisinin olduğu, mikrobiyotanın sindirim, endokrin sistem, nöral ve immün yollar aracılığıyla inflamasyonun düzenlenmesi gibi önemli fonksiyonel görevlerinin olduğu da bulunmuştur (8,11,12). İnsan sağlığını prenatal dönemden başlayarak etkilemeye başlayan mikrobiyota birçok açıdan önem taşımakta olup, önemine yönelik yapılan çalışmalar literatürde yeni yeni artmaktadır (10). Ancak yenidoğanda mikrobiyota gelişimine etki eden faktörlerin ve bu faktörlerin etkilerinin bilinmesi, yenidoğan sağlığına etkilerinin değerlendirilmesi ve olumsuz etkilerinin önlenmesine yönelik çalışmaların yapılabilmesi için daha fazla araştırmaya ihtiyaç duyulmaktadır (5,8). Dolayısıyla yenidoğan mikrobiyotası ve yenidoğan mikrobiyotasını etkileyen faktörlerin bilinmesi ve konu ile ilgili derleme niteliğinde literatüre kaynak oluşturulması önem arz etmektedir. Bu nedenle bu derlemenin amacı; yenidoğan mikrobiyotası ve yenidoğan mikrobiyotasını etkileyen faktörlerin güncel literatür ışığında değerlendirmektir.

Yenidoğan Mikrobiyotası

Son dönemde yenidoğan mikrobiyotasının kaynağı hakkında mevcut teorilerin bulunmasına karşın kesin bilgi bulunmamaktadır. Bazı çalışmalarda ilk mikrobiyal kolonizasyonun fetüsün doğum kanalından geçmesiyle gerçekleştiği belirtilirken, bazı çalışmalarda da başta gastrointestinal sistem olmak üzere, fetüsün mikroorganizmalarla karşılaşmasının doğumdan önce uterusta başladığı, mekonyum örnekleri ve amniyotik sıvı örneklerinde mikrobiyota yapısının bulunduğu ve gelişmekte olan fetal bağışıklık sistemini etkileme potansiyeline sahip olduğu ifade edilmiştir (8,13). Doksanlı yıllara doğru fetüsün steril bir ortamda geliştiği düşüncesi hakimken, son yıllarda yapılan çalışmalarda fetüsün intrauterin yaşamda steril bir ortamda olmadığı, oosit toplama sırasında alınan folikül sıvılarının mikrobiyal bir floraya sahip olduğu, bakterilerin plasenta aracılığıyla fetüse ulaştığı ve bu bakteri grubunun oral flora bakterileriyle benzerlik gösterdiği kabul edilmiştir (14-16). Ayrıca yenidoğan mikrobiyotasının oluşumunda çeşitli faktörler rol oynarken en fazla etkiyi anne mikrobiyotasının oluşturduğu gösterilmiştir (5,17,18). Yenidoğan mikrobiyotasını etkileyen başlıca faktörler "gebelik süresi, vajinal mikrobiyota ve doğum şekli, yenidoğanın beslenme şekli, anne sütü alma durumu, maternal beslenme şekli, maternal ağırlık kazanımı ve obezite, maternal ilaç kullanımı" başlıkları altında aşağıda ele alınmıştır.

Gebelik Süresinin Yenidoğan Mikrobiyotasına Etkisi

Yenidoğanın özellikle bağırsak mikrobiyotasının oluşumunu etkileyen önemli faktörlerden biri de annenin gebelik süresidir. Zamanında ve erken doğan yenidoğanların mikrobiyotalarının karşılaştırıldığı çalışmalarda, term ve preterm yenidoğanların mikrobiyotalarında önemli farklılıkların olduğu görülmüştür (18). Ayrıca prematüre bebeklerin mikrobiyotasında Enterobacteriaceae Clostridium difficile ve Klebsiella pneumoniae gibi patojenik bakterilere zamanında doğan bebeklere göre daha fazla rastlandığı, zamanında doğan bebeklerde dışkı mikrobiyotası çeşitliliğinin daha yüksek olduğu ve Bifidobacterium, Lactobacillus ve Streptococcus gibi yararlı mikrobiyota türlerine daha çok rastlandığı sonuçlarına ulaşılmıştır (19). Yapılan başka çalışmalarda da zamanında doğum yapan kadınlardan alınan kolostrum örneklerinde, Bifidobacterium türüne ait yararlı bakterilerin yüksek, Enterococcus türüne ait zararlı bakterilerin ise düşük düzeyde olduğu, zamanında doğan yenidoğanlarda yararlı mikrobiyota çeşitliliğinin arttığı saptanmıştır (15,20).

Vajinal Mikrobiyota ve Doğum Şeklinin Yenidoğan Mikrobiyotasına Etkisi

Vajinal mikrobiyomdan ilk olarak 1892 yılında Albert Döderlein'in "Vajinal Salgılar" adlı yazısında bahsedilmiş ve sağlıklı kadınların vajinal salgılarında yararlı mikrobiyota yapısının bulunduğuna değinilmiştir (3). Günümüzde vajinal sağlık için Lactobacillus türlerinin ve asidik ortamın varlığının önemli olduğu kabul görmektedir (21). Genel olarak vajinal mikrobiyotanın oluşumu değişken bir süreç olmakla birlikte, kadınlar arasında zaman içerisinde farklılıklar ortaya çıkabilmektedir. Vajinal mikrobiyota; etnik köken, gebelik, adet döngüsü, cinsel aktivite ve çevresel değişimler gibi birçok faktörden etkilenebilmektedir (5,22).

Normal vajinal doğum şekli ile yenidoğana geçen vajinal mik-

robiyotanın, yenidoğan mikrobiyotası üzerinde önemli etkiye sahip olduğu, bakterilere karşı koruyucu rol oynadığı, bağırsakların bariyer fonksiyonu ve immün sistemin gelişimini desteklediği bilinmektedir (23). Dolayısıyla doğum şekli yenidoğan mikrobiyotasının yapılanmasında rol oynayan en önemli etkenler arasında yer almakta olup, normal vajinal doğum ile doğan yenidoğanın mikrobiyotası maternal vajinal mikrobiyoma benzeyen bakteri topluluklarını içerirken, sezaryen doğum ile doğanların mikrobiyota yapısı, maternal cilt mikrobiyotasına benzemektedir (4). Yapılan çalışmalarda; sezaryen doğumlarda yenidoğanın bağırsak mikrobiyotasının anne derisi ve hastane kaynaklı alanlara benzer mikroorganizma içerdiği, yenidoğanın gaytasında bazı yararlı bakterilerin az olduğu veya hiç olmadığı, yenidoğan mikrobiyotasındaki bu farklılığın ileriki yaşam dönemlerinde de devam ettiği belirlenmiştir (24,25). Ayrıca yenidoğanlarda sezaryen doğuma bağlı olarak, maternal vajinal ve bağırsak florasıyla olan temas eksikliği sonucu çeşitli risk faktörlerinin arttığı, anne sütünden mikrobiyota geçişinin de olumsuz etkilendiği belirtilmiştir (26). Son zamanlarda sezaryenle doğan yenidoğanın, annenin vajinal sıvısıyla doğumdan hemen sonra temas ettirilmesi şeklinde, vajinal tohumlama (vajinal seeding) olarak adlandırılan uygulamanın yararlı olduğu belirtilmektedir. Ancak bu uygulamanın neonatal enfeksiyon riski oluşturabileceği ve barsak mikrobiyotasını olumsuz etkileyebileceğinden dolayı önerilmemektedir (27).

Yenidoğan Beslenme Şeklinin Yenidoğan Mikrobiyotasına Etkisi

Anne sütünün bebeklerin mikrobiyota üzerine etkisi yüzyıllar öncesinde belirtilmiş olup, anne sütünün içerisindeki yararlı bakterilerin bebeğin intestinal mikrobiyotasının en önemli kaynağı olduğunu gösterilmiştir. Anne sütü mikrobiyota içeriği bakımından bebeğin mikrobiyotasının gelişimi için en önemli belirleyici ve en etkili besin maddesidir (5,8). Yenidoğan anne sütü ile beslenmeye başladığında kendi mikrobiyotasına ek olarak, anne sütü içerisinde yer alan mikrobiyotayı ve kendi mikrobiyotasını besleyen ve zararlı mikroorganizmalardan koruma görevi gören prebiyotikleride alır (7,28). Anne sütünün bileşiminde başlangıçta Weissella, Leuconostoc, Staphylococcus, Streptococcus ve Lactococcus türlerinin baskın olarak yer aldığı, "daha sonra ise Veillonella, Prevotella, Leptotrichia, Lactobacillus, Streptococcus ve Bifrobaccoum türlerin yer aldığı gösterilmiştir. Laktasyon dönemi boyunca da bu bileşimin değiştiği ve bu içeriğin coğrafi bölgeler, etnik farklılıklar, anneye ve bebeğe ait faktörler gibi bazı değişikliklerden etkilendiği belirtilmektedir (7,12,29).

Yenidoğanlarda sağlıklı mikrobiyota gelişiminin altın standardı olarak kabul edilen anne sütü, içerdiği yararlı bakteriler aracılığıyla patojenlere karşı koruma ve yenidoğanın, mikrobiyotası içeriğinde kısa sürede çeşitlenme sağladığı, yenidoğanın farklı ihtiyaçlarına yönelik cevap oluşturduğu gösterilmiştir (2). Amerika Birleşik Devletleri, Almanya ve Finlandiya'da 1000'e yakın bebeğin ilk üç yılında mikrobiyotası üzerine etkili faktörlerin değerlendirildiği çalışmada; intestinal mikrobiyotası üzerine etkili faktörler arasında en belirleyici etkiyi anne sütü ile beslenmenin oluşturduğu, sadece anne sütü ile beslenen bebeklerin bağırsaklarında %80'e yakın oranda yararlı bakterilerin bulunduğu bir mikrobiyota olduğu belirtilmiştir (1). Anne sütünde bulunun mikrobiyotanın başta immün faktörden etkilenen hastalıklar olmak üzere birçok hastalığa karşı koruyucu etkisi olduğu düşünülmekte ve özellikle ilk ay bebeklerin emzirilmesi ve sadece anne sütü ile beslenilmesi önerilmektedir (7,9). Çünkü anne sütü dışındaki besinlerle beslenen bebeklerin çeşitli patojen mikroorganizmalara ve enfeksiyonlara karşı daha hassas bir yapıya sahip olduğu bilinmektedir. Yenidoğanın anne sütü ile beslenmesini ve emzirmenin sürdürülebilir olmasını sağlamak, anneleri bu yönde desteklemek için doğum sonrasında erken dönemde destekleyici olunmalı, emzirme sürecinin iyi yönetilmesi sağlanmalı, emzirme yetersizliğine ve başarısızlığına yol açan nedenler belirlenmeli, bebeklerin doğumdan sonraki ilk altı ay sadece anne sütü ile beslenerek en az iki yaşına kadar anne sütü almaları sağlamalıdır (4,30).

Maternal Beslenme Şeklinin Yenidoğan Mikrobiyotasına Etkisi

Maternal beslenme şekli vajinal, bağırsak ve anne sütü mikrobiyotası üzerinde oldukça etkilidir ve böylelikle yenidoğanın mikrobiyotasını doğrudan etkilemektedir. Aynı zamanda maternal beslenme mikrobiyal çeşitliliği, bağırsak mikrobiyota yapısını ve fonksiyonunu etkileyebilmektedir. Bu nedenle gebelik ve emzirme dönemlerinde prebiyotik ve probiyotik içeren gıdalara maternal diyette yer verilmesi, sağlıklı mikrobiyota içeren besinler yönünden zengin beslenilmesi, annenin mikrobiyotası üzerindeki yarattığı olumlu etkinin yanında yenidoğan mikrobiyotası üzerinde de olumlu etki yaratacaktır (5-7). Konu ile ilgili yapılan çalışmalarda, dengeli ve yeterli bir maternal beslenme ile anne sütü alan bebeklerde bağışıklık sisteminin geliştiği, mikrobiyota kompozisyonunun çeşitlendiği, yüksek lif ve bitkisel polisakkaritlerden zengin beslenmenin mikrobiyal çeşitliliği olumlu yönde arttırdığı, tam tahılların kısa süreli alımının bağırsak mikrobiyotasında olumlu değişikliklere neden olduğu belirtilmiştir. Ayrıca gebelik ve emzirme dönemlerinde alkol ve fazla kafein içeren

içeceklerin, zararlı maddelerin alımının yenidoğanda mikrobiyal gelişimi ve çeşitliliği etkilediği, mevcut mikrobiyotaya zarar verdiği, annenin beslenme şeklinin yenidoğan mikrobiyotasını etkilediği gösterilmiştir (13,14,31).

Maternal Ağırlık Kazanımı ve Obezitenin Yenidoğan Mikrobiyotasına Etkisi

Maternal obezite, anne sütünde bulunan mikrobiyal çeşitliliğin azalmasına, mikrobiyota yapısının bozulmasına yol açmaktadır. Maternal ağırlık kazanımının, yenidoğanın bağırsak mikrobiyotası üzerindeki etkileri inceleyen çalışmalarda da gebelik dönemindeki ağırlık kazanımının yenidoğan bağırsak mikrobiyotası üzerinde olumsuz yönde etkili olduğu belirtilmiştir (3,32). Gebelerde bağırsak mikrobiyotası ile vücut ağırlığı ve ağırlık kazanımı arasındaki ilişkiyi inceleyen bir çalışmada; fazla kilolu gebelerde Staphylococcus, Enterobacteria ve Esherichia Coli türlerinin normal kilolu gebelere oranla arttığı, yararlı mikrobiyotanın fazla kilolu gebelerde azalma eğilimi gösterdiği belirlenmiştir (27). Gebelikte maternal obezitenin etkisini inceleyen bir çalışmada, obez gebeliklerde intestinal disbiyozis geliştiği ve bunun da fetüsün gelişimini olumsuz etkileyebilecek metabolik değişimlere neden olduğu gösterilmiştir. Diğer bir çalışmada ise; yüksek yağlı diyet ile beslenenlerde bağırsak mikrobiyal yapısında bozulma ve çeşitliliğinde azalma ile bebeklerin bağırsak mikrobiyota değişikliklerinin bağlantılı olduğunu gösterilmiştir (28). Ayrıca diğer çalışmalardan elde edilen bulgulara göre; gebelik süresince yüksek yağlı bir diyet ile beslenmenin, yenidoğanın bağışıklık sistemi üzerine uzun süreli etkiler oluşturabileceği ve mikrobiyota yapısının bozulmasıyla yenidoğanın obeziteye ve metabolik hastalıklara daha yatkın olabileceğini belirtilmektedir (17,25).

Maternal İlaç Kullanımının Yenidoğan Mikrobiyotasına Etkisi

İlaç kullanımı hastalıkların tedavisi, kontrolü ve önlenmesinde önemli bir role sahipken, gebe, emziren anne, fetüs ve yenidoğan mikrobiyotasında olumsuz etki ve değişikliklere neden olabilmektedir (15,33). Özellikle gebelikte antibiyotik gibi ilaçların uygunsuz kullanımının, bağırsağın yapısında bulunan mikrobiyal çeşitliliğinin azalmasına yol açtığı, metabolik kapasiteyi değiştirerek zararlı patojenlerin çoğalması süreçlerini içeren disbiyozise neden olduğu, bunun sonucunda da astım, epilepsi ve obezite gibi çeşitli hastalık riskinde artış yaşandığını vurgulanmaktadır. Ayrıca literatürde, gebelikte antibiyotiğe maruz kalan bebeklerde obezite görülme riskinin, bel çevresi ve vücut yağ yüzdesinin önemli ölçüde arttığını gösteren çalışmalarda bulunmaktadır (30). Bu nedenle antibiyotik gibi mikrobiyota üzerine çeşitli olumsuz etki gösteren ilaçların fetüsün ya da yenidoğanın mikrobiyotasında ortaya çıkartacağı olumsuzluklar nedeniyle, doktor kontrolünde alınması ve dar spektrumlu tercih edilmesi önerilmektedir. Bu konuda annenin bilgilendirilmesi ve akılcı ilaç kullanımı konusunda anneye danışmanlık verilmesi önemlidir (12,34).

Yenidoğanda Mikrobiyotanın Olumsuz Yönde Gelişmesi ve Sağlık Sorunları

Mikrobiyotanın yenidoğan sağlığı, gelişimi, fizyolojisi ve bağışıklığı üzerinde son derece önemli bir etkiye sahip olduğu, yenidoğan döneminden başlayarak mikrobiyotanın olumsuz yönde gelişmesinin, tüm yaşam boyu devam eden birtakım sağlık sorunlarına neden olduğu belirtilmektedir (4,33). Mikrobiyotasındaki değişimler intrauterin yaşamın başlangıcından itibaren yenidoğanı önemli derece etkilemekte, yenidoğan sağlığı ve hastalıklarında önemli rol oynamaktadır (13). Ayrıca yapılan çalışmalar, barsak mikrobiyotasının beyin nörokimyasını nöral, immün ve endokrin mekanizmalar gibi çeşitli mekanizmalar yoluyla direkt veya indirekt olarak değiştirebildiği, barsak mikrobiyotasının konağın metabolizmasını, besin emilimini ve immün fonksiyonlarını etkilediği, bu dengenin bozulmasının çok ciddi sağlık etkileri oluşturabileceği vurgulamaktadır (18,35,36). Bu nedenle mikrobiyotanın sağlık üzerine etkilerini kanıtlamaya yönelik yapılan çalışmalar gün geçtikçe artmaktadır. Olumlu yönde gelişen mikrobiyota, bağışıklık sisteminin desteklenmesinin yanı sıra beyin faaliyetleri gibi vücut fonksiyonlarının yerine getirilmesinde önemli roller üstlenmektedir (18). Dolayısıyla yenidoğanda sağlıklı bir mikrobiyota, bağışıklık sisteminin güçlü olması ve kommensal mikroorganizmalar ile erken etkileşim sonucu uzun vadede sağlıklı bağışıklık gelişimiyle ilişkilendirilmektedir. Bunun yanında, yapılan çalışmalarda, yenidoğan mikrobiyotasının olumsuz yönde gelişmesi ile obezite riski, bağışıklık sistemi bozukları, astım, alerji ve immün yetmezlik riski arasında ilişki olduğu bildirilmiştir (32-34). Mikrobiyotanın konakçı immün sistemine son derecede önemli destek olmasına rağmen mikrobiyotadaki anormal değişiklikler neticesinde gelişen disbiyozis durumunda ise diyabet, inflamatuar hastalıklar, metabolik sendrom, irritabl barsak sendromu ve kanser gelişimi hızlanmaktadır (35,36). Ayrıca son zamanlarda yapılan çalışmalar, mikrobiyotayı, viral enfeksiyonun karsinogenezi teşvik etme kabiliyetini arttırarak veya azaltarak bu dengeyi etkileyebilen potansiyel ve kritik bir faktör olarak ortaya koymuştur (34,37).

SONUÇ VE ÖNERİLER

Son zamanlarda mikrobiyota çeşitliliği ve miktarının önemini bildiren çalışmaların artması, mikrobiyotadaki değişimlerin hem annenin hem de yenidoğanın sağlığına etkilerinin anlaşılması, mikrobiyotanın işlevini, fayda ve zararlarını anlamayı zorunlu kılmaktadır. Mikrobiyota intrauterin yaşamın başlangıcından itibaren insan sağlığını önemli derece etkilemektedir. Bu nedenle yenidoğanda yararlı mikrobiyota gelişimini etkileyen faktörlerin üzerinde durulması ve mikrobiyota gelişimini olumsuz etkileyen faktörlerin ortadan kaldırılması gerekmektedir. Ayrıca mikrobiyotanın yenidoğan sağlığına etkilerinin değerlendirilmesine yönelik fazla araştırmaya ihtiyaç duyulmaktadır. Gebelik, doğum ve emzirmenin mikrobiyota ile ilişkisinin daha çok anlaşılması, gelecekteki yaşam kalitesinin artırılması, anne ve yenidoğan sağlığının gelişmesi noktasında yarar sağlayacaktır. Toplumun sağlığını geliştirmek için önemli role sahip olan sağlık profesyonellerinin prenatal dönemden başlayarak fetüs ve yenidoğan mikrobiyotasını etkileyecek durumlar üzerinde durması, vajinal normal doğumu destekleyen bir yaklaşımın benimsenmesi, yenidoğanın erken dönemde ve en az iki yaşına kadar emzirilmesinin sağlanması, kadınların akılcı ilaç kullanımı, sağlıklı maternal beslenme ve uygun ağırlık kazanımı ile maternal obezitenin önlenmesine yönelik konularda desteklenmesi sağlıklı nesillerin ortaya çıkmasında önem arz etmektedir.

Yazarın Katkı Beyanı

Fikir/Kavram, Tasarım, Denetleme/Danışmanlık, Kaynak Taraması, Makalenin Yazımı: RD şeklindedir.

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