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Bu sayımızda da birbirinden değerli 23 bilimsel metne yer verdik. Obstetri alanında 7 orijinal makale, 1 editöre mektup ve 1 olgu sunumu; onkoloji alanında 6 orijinal makale, 1 derleme, 1 tez özeti; jinekoloji alanlarına ait 4 orijinal araştırma makalesi; infertilite ve yenidoğan alanına ait 1'er orijinal makalesini sizlerin beğenisine sunduk.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Türkiye'deki Suriyeli göçmen gebe kadınların doğum özellikleri ve obstetrik sonuçlarının Türkiyeli gebe kadınların sonuçları ile karşılaştırılması

Comparison of birth characteristics and obstetric outcomes of Syrian immigrant pregnant women in Türkiye with the results of pregnant women in Türkiye

Güldeniz TOKLUCU[1], Bilge DOĞAN TAYMUR[1]

[1]Şehit Prof. Dr. İlhan Varank Sancaktepe Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Sağlık Bilimleri Üniversitesi, İstanbul, Türkiye

ÖZ

Amaç: Dünyada ülkeler arası artan göçler nedeniyle göçmen sağlığı önem kazanmıştır. Göçün sağlık üzerindeki etkisi; başta sosyodemografik ve ekonomik olmak üzere geniş kapsamlı değerlendirilmelidir. Çalışmanın amacı Türkiye'deki Suriyeli mülteci kadınların doğum öncesi bakım, gebelik ve yenidoğan sonuçlarını değerlendirmek ve yerel halkla karşılaştırmaktır.

Gereç ve Yöntemler:: Eylül 2020-Ekim 2021 tarihleri arasında Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 5113 gebe retrospektif olarak tarandı. Gruplar demografik veriler, obstetrik özellikler ve gebelik sonuçları açısından karşılaştırıldı.

Bulgular: Türkiye vatandaşı olan olguların yaşları, Suriyeli olguların yaşlarından istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır (p=0,001; p0,05). Suriyeli olguların daha önce yaptığı sezaryenle doğum sayısı, Türkiye vatandaşı olanlardan istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır (p=0,009; p0,05). Çalışmamızda doğum şekilleri incelendiğinde göçmen popülasyonda normal doğum oranı daha yüksek bulunmuştur. Sezaryen doğum oranları Türkiye toplumunda daha yüksek saptanmıştır ancak sezaryen endikasyonları açısından iki grup arasında fark saptanmadı.

Sonuç: İklim değişiklikleri, savaşlar, ekonomik sorunlar gibi nedenlerle oluşabilen göçler sonucunda göçmenlere göç ettikleri yerin sosyokültürel yapısı göz önüne alınarak tamamlayıcı sağlık hizmeti verilmelidir. Çalışmamızdan elde ettiğimiz veriler sonucunda Türkiye devletinin mülteci sağlığı politikalarının olumlu sonuç verdiği görünmektedir. Kliniğimizde normal doğumu destekleyen sağlık uygulamalarını benimsediğimiz için sonuçlarımızın olumlu olduğunu düşünmekteyiz. Bu sağlık hizmeti hem göç eden halkın hem göç alan halkın tamamlayıcı, bütünleyici bir şekilde bir arada yaşamalarına imkan verir.

Anahtar Kelimeler: Göçmen sağlığı, obstetrik sonuçlar, Suriyeli göçmen

ABSTRACT

Aim: Migranthealth has gained importance due to the increasing migration between countries in the world. The impact of migration on health should be evaluated comprehensively, especially sociodemographically and economically. The aim of the study was to evaluate the prenatal care, pregnancy, and new born outcomes of Syrian refugee women in Turkey and compare them with the local population.

Materials and Methods: Between September 2020 and October 2021, 5113 pregnant women who applied to the Gynecology and Obstetrics Clinic of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital were retrospectively screened. The groups were compared in terms of demographic data, obstetric characteristics, and pregnancy outcomes.

Results: The ages of the cases who were citizens of Turkey were found to be statistically significantly higher than the ages of the Syrian cases (p=0.001; p<0.01). The number of surviving infants of Syrian cases was found to be statistically significantly higher than the number of surviving in fants of Turkish citizens (p=0.001; p<0.01). There was no statistically significant difference in the number of previous curettages and abortions according to the groups (p>0.05). The number of previous cesarean deliveries in Syrian cases was found to be statistically significantly higher than that of Turkish citizens (p=0.009; p<0.01). Thenumber of normal births in Syrian cases was found to be statistically significantly higher than that of Turkish citizens (p=0.001; p<0.01).

Conclusion: As a result of migrations that may occur due to reasons such as climate change, wars, and economic problems, complementary health services should be provided to immigrants, taking into account the sociocultural structure of the place they migrated to. As a result of the data we obtained from our study, it seems that the refugee health policies of theTurkish state have yielded positive results. We think that our results are positive because we have adopted health practices that support normal birth in our clinic. This health service allows both the migrant and the receiving people to live together in a complementary manner.

Keywords: Migranthealthcare, obstetricoutcomes, Syrianmigrant

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Sorumlu Yazar/Corresponding Author: Güldeniz TOKLUCU, Şehit Prof. Dr. İlhan Varank Sancaktepe Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Sağlık Bilimleri Üniversitesi, İstanbul, Türkiye
E-mail: guldeniztoklucu@gmail.com

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GİRİŞ

İklim değişiklikleri, savaşlar, sivil karışıklıklar, ekonomik sorunlar gibi nedenlerle global olarak göçmenlerin sayısı her yıl artmaya devam etmekte ve dünyadaki çoğu ülke bu durumla mücadele etmek durumunda kalmıştır. (1). Birleşmiş Milletler (BM) verilerine göre, 2011'den bu yana güvenliğin azalması nedeniyle, 5,8 milyondan fazla insan Suriye'den Lübnan'a, Türkiye'ye, Ürdün'e ve diğer ülkelere göç etmek zorunda kaldı ve milyonlarca insan Suriye içinde yer değiştirdi (2). Suriye savaşı, yakın tarihte büyük bir göçe neden olmuştur. Türkiye, Suriye'nin en önemli ve en büyük komşusu olduğundan en fazla Suriyeli mülteci Türkiye'de ikamet etmektedir. Temmuz 2023 tarihinde Göç İdaresi Başkanlığı'nın yaptığı açıklamada ise ülke genelinde toplam göçmen sayısı 3 milyon 329 bin 519 kişi olarak belirtilmiştir. Türkiye'deki tüm Suriyeli mültecilerin %47,3'ü kadındır. Göçün sağlık üzerindeki etkisi geniş kapsamlıdır, göçmen nüfusları özellikle sağlık hizmeti almakta sorun yaşamakta, bu durum sağlık eşitsizliklerini körüklemekte ve küresel sağlık için ciddi etkilere yol açmaktadır (3).

Göç, sağlığın önemli bir sosyal belirleyicisidir (4). Kadınların hayatında zorlu bir süreç olan gebelik, mülteciler için daha da zorlayıcı bir hale gelmektedir. Gebe mülteci kadınlar üzerinde yapılan önceki çalışmaların bazıları, gebeliğe bağlı komplikasyonların ve neonatal komplikasyonların arttığını ileri sürerken bazılarında, Türkiye vatandaşı ve Suriyeli göçmenlerin gebelikleri karşılaştırılmış ve belirgin bir ayrım bulunamamıştır (5-10). Göçmen popülasyonlarında gebelik ve sonuçlarının komplikasyonlarının artmasının etkenleri arasında; sağlık hizmetlerine erişimdeki zorluklar, beslenme sorunları, ülke koşulları gibi çevresel faktörler, mülteci nüfusun gebeliğe bakış açısı, genetik faktörler ve önceki gebelik yönetimi ve doğum yöntemlerinden farklılıklar gibi birçok faktör vardır (11).

Çalışmamız, gebe Suriyeli mültecilerin doğum öncesi, doğum ve yenidoğan sonuçlarını sunmayı ve sonuçları gebe Türkiye vatandaşları ile karşılaştırmayı amaçlamaktadır

GEREÇ VE YÖNTEM

Eylül 2020-Ekim 2021 tarihleri arasında Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 5113 gebe retrospektif olarak tarandı. Bu çalışmaya 20 gebelik haftasından sonra doğum yapmış, olan ve doğum sonrası muayenesi çocuk doktorlarımız tarafından yapılan 18 yaş üstü gebeler dahil edildi. Hastane bilgi sisteminde eksik veriye sahip gebeler çalışma dışı bırakıldı.

İstatistiksel İncelemeler

İstatistiksel analizler için NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) programı kullanıldı. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodlar (ortalama, standart sapma, medyan, frekans, yüzde, minimum, maksimum) kullanıldı. Nicel verilerin normal dağılıma uygunlukları Shapiro-Wilk testi ve grafiksel incelemeler ile sınanmıştır. Normal dağılım gösteren nicel değişkenlerin iki grup arası karşılaştırmalarında Bağımsız gruplar t testi, normal dağılım göstermeyen nicel değişkenlerin iki grup arası karşılaştırmalarında Mann-Whitney U test kullanıldı. Nitel verilerin karşılaştırılmasında Pearson ki-kare test, Fisher'sexact test, Fisher-Freeman-Haltonexact test kullanıldı. İstatistiksel anlamlılık $p<0.05$ olarak kabul edildi.

BULGULAR

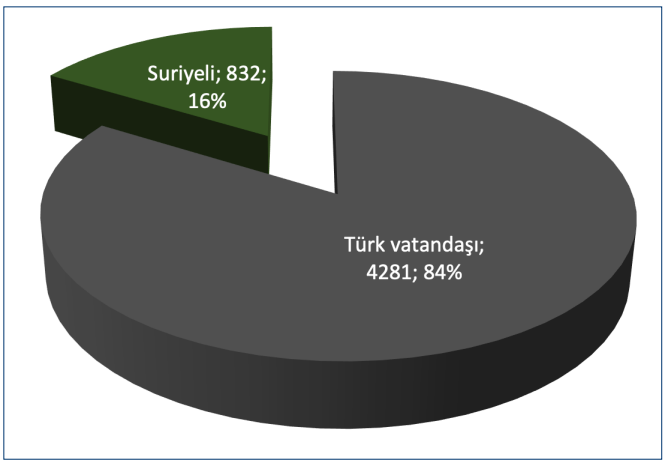
Araştırma 01 Eylül 2020 - 01 Eylül 2021 tarihleri arasında Şehit Prof. Dr. İlhan Varank Sancaktepe Eğitim ve Araştırma Hastanesi'nde toplamda 5113 olguyla yapılmıştır. Olguların %16'sı Suriyeli göçmenlerden oluşurken %84'ü Türkiye vatandaşıydı (Şekil1).

Türkiye vatandaşı olan olguların yaşları, Suriyeli olguların yaşlarından istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır ($p=0,001$; $p<0,01$).

Türkiye vatandaşı olan olguların bebeklerinin boyları, Suriyelilerinkinden istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır ($p=0,026$; $p<0,05$).

Türkiye vatandaşı olan olguların bebeklerinin ağırlıkları, Suriyelilerin bebeklerinin ağırlıklarından istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır ($p=0,001$; $p<0,01$).

Gruplara göre olguların doğum durumları arasında istatistiksel olarak anlamlı farklılık saptanmamıştır ($p>0,05$).



Şekil 1. Grupların dağılımı

Tablo 1. Gruplara Göre Değerlendirmeler

		Türkiye vatandaşı	Suriyeli	P
Anne yaş				**[a]0,001****
	Medyan (Min-Maks)	28 (15-51)	25 (18-44)	
Bebek boy (cm)			50,12±2,87	**[a]0,026***
	Medyan (Min-Maks)	50 (23-60)	50 (12-57)	
Bebek ağırlık (gr)				**[a]0,001****
	Medyan (Min-Maks)	3285 (400-4870)	3220 (300-5150)	
Baş çevresi (cm)				**[b]0,001****
	Medyan (Min-Maks)	35 (12-40)	35 (5-40)	
Doğum şekli	Normal doğum	2593 (60,6)	581 (69,8)	**[c]0,001****
	Sezaryen/müdahaleli doğum	1688 (39,4)	251 (30,2)	
Doğum durumu	Canlı doğum	4241 (99,4)	826 (99,3)	**[d]0,618**
	Ölü doğum	24 (0,6)	6 (0,7)	
Gebelik sayısı				**[b]0,001****
	Medyan (Min-Maks)	2 (1-11)	3 (1-10)	
Sezaryen nedeni	Baş pelvis uyumsuzluğu	14 (0,8)	0 (0)	**[e]0,180**
	Çoğul gebelik	50 (3,0)	16 (6,4)	
	Fetal sıkıntı	199 (11,8)	28 (11,2)	
	Gebeliğin hipertansif hastalıkları (Preeklemsi, eklemsi, gebelik+HT)	33 (2,0)	5 (2,0)	
	Geçirilmiş uterin cerrahi (Sezaryen ve diğer)	1084 (64,1)	164 (65,6)	
	İri bebek	117 (6,9)	10 (4,0)	
	Plasenta anomalileri (Pl.dekolmanı, Pl.Previa dahil)	14 (0,8)	2 (0,8)	
	Prezantasyon anomalileri (Makat, alın, transvers, yüz gibi)	96 (5,7)	16 (6,4)	
	Uzamış eylem	33 (2,0)	3 (1,2)	
	Diğer	50 (3,0)	6 (2,4)	

[a]Student t Test
[b]MannWhitney U Test [c]ChiSquare Test [d]Fisher'sExact Test [e]FisherFreemanHalton Test *p<0,05
***p<0,01*

Türkiye vatandaşı olan olguların bebeklerinin baş çevresi ölçümleri, Suriyelilerin bebeklerinin baş çevresi ölçümlerinden istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır (p=0,001; p<0,01).

Suriyeli olguların normal doğum yapma oranı daha yüksekken, Türkiye vatandaşı olanların sezaryen –müdahaleli doğum yapma oranı istatistiksel olarak anlamlı düzeyde daha yüksektir (p=0,001; p<0,01).

Suriyeli olguların ölü doğum oranı ile Türkiye vatandaşları arasında istatistiksel olarak anlamlı fark saptanmamıştır (p>0,05).

Suriyeli olguların gebelik sayıları, Türkiye vatandaşı olanlardan istatistiksel olarak anlamlı düzeyde daha yüksek saptanmıştır (p=0,001; p<0,01).

Gruplara göre olguların sezaryen nedenleri arasında istatistiksel olarak anlamlı farklılık saptanmamıştır (p>0,05).

Suriyeli olguların daha önce yaptığı normal doğum sayısı, Türkiye vatandaşı olanlardan istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır (p=0,001; p<0,01).

Suriyeli olguların daha önce yaptığı sezaryenle doğum sayısı, Türkiye vatandaşı olanlardan istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır (p=0,009; p<0,01).

Gruplara göre olguların daha önceki küretaj ve abortus sayıları istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05).

TARTIŞMA

Göçün sağlık üzerindeki etkisi başta sosyodemografik ve ekonomik olmak üzere geniş kapsamlıdır, dolayısıyla küresel sağlık için ciddi sonuçlara yol açmaktadır. Uluslararası bir problem olarak karşımıza çıkan ve giderek artan göçler, sosyal, kültürel, ekonomik ve fiziksel olarak tüm toplumu etkilemektedir. Ayrıca toplum sağlığı ve sağlık değişkenlerini de olumsuz etkilemektedir (12). Mülteci kadınların gebelikten korunma, doğum öncesi- doğum ve doğum sonrası

Tablo 2. Önceki Doğum Bilgilerinin Gruplara Göre Değerlendirilmesi

		Türkiye vatandaşı	Suriyeli	P
Normal doğum sayısı				**[b]0,001****
	Medyan (Min-Maks)	0 (0-8)	1 (0-8)	
	Yok	2104 (50,2)	303 (36,5)	
	1	1466 (35)	203 (24,5)	
	2	377 (9)	178 (21,4)	
	3	149 (3,6)	85 (10,2)	
	4	60 (1,4)	37 (4,5)	
	≥5	35 (0,8)	24 (2,9)	
Sezaryenle doğum sayısı				**[b]0,009****
	Medyan (Min-Maks)	0 (0-4)	0 (0-5)	
	Yok	3109 (74,2)	665 (80,2)	
	1	825 (19,7)	73 (8,8)	
	2	191 (4,6)	57 (6,9)	
	3	65 (1,6)	28 (3,4)	
	≥4	1 (0)	6 (0,7)	
Küretaj sayısı				**[b]0,071**
	Medyan (Min-Maks)	0 (0-1)	0 (0-3)	
	Yok	4189 (100)	827 (99,8)	
	≥1	2 (0)	2 (0,2)	
Abortus sayısı				**[b]0,744**
	Medyan (Min-Maks)	0 (0-4)	0 (0-5)	
	Yok	3900 (93,1)	774 (93,4)	
	1	215 (5,1)	42 (5,1)	
	2	56 (1,3)	7 (0,8)	
	≥3	20 (0,5)	6 (0,7)	
Yaşayan bebek sayısı				**[b]0,001****
	Medyan (Min-Maks)	1 (0-8)	1 (0-8)	
	Yok	1069 (25,5)	167 (20,2)	
	1	2244 (53,5)	248 (30)	
	2	543 (13)	215 (26)	
	3	224 (5,3)	122 (14,7)	
	4	72 (1,7)	49 (5,9)	
	≥5	39 (0,9)	27 (3,3)	

[b]MannWhitney U Test
*p<0,05
**p<0,01

bakım, vitamin ve mineral eksiklikleri, istenmeyen gebelik, düşük, doğum komplikasyonları gibi üreme sağlığı ve aile planlaması konularında yetersiz bilgiye sahip oldukları görülmektedir (13).

Çalışmamızın amacı Türkiye'deki Suriyeli mülteci kadınların doğum öncesi bakım, gebelik ve yenidoğan sonuçlarını değerlendirerek ve yerel halkla karşılaştırarak tamamlayıcı sağlık hizmetlerinin yeterliliğini değerlendirmektir.

Çalışmamızda Türkiye vatandaşıgebelerde yaş ortalaması, boy ortalaması ve bebek boy ortalaması Suriyeli mültecilere göre daha yüksek saptanmıştır. Yenidoğanların doğum ağırlıkları Suriyeli mültecilerin yenidoğanlarında d2022 yılında yayınlanan 4992 Suriyeli mülteci aha düşük saptanmıştır. Bu farklılıkların şu durumlardan kaynaklanabileceği düşünülebilir: Suriyeli kadınların arasında beslenme yetersizliği ve doğum öncesi bakımın yetersiz olması veya konstütisyonel kısalık. Bursa'da yapılan bir çalışmada Suriyeliler arasında okuma yazma bilmediğini bildiren kadınların oranının Türklere göre daha yüksek olduğu tespit edilmiştir. Eğitim düzeyi de sağlıklı beslenme ve yaşam alışkanlıklarını etkileyerek anne ve bebek boyunun daha düşük saptanma nedenlerinden olabilir (8-10). Türkiye'ye yerleşen Suriyeli mültecilerle ilgili daha önce yapılan çalışmalardan elde edilen mevcut kanıtları destekleyerek, kültürel farklılıkların anne yaşını etkileyen önde gelen faktörler olduğunu düşünüyoruz (8-13). 2022 yılında yayınlanan 4992 Suriyeli mülteci ve 6846 Türkiye vatandaşıgebeden oluşan 6 yıllık retrospektif kesitsel bir çalışmada Suriyeli göçmen kadınlarda yaş

ortalaması ve doğum sonu komplikasyon oranı daha düşük, normal doğum ve SGA oranı daha yüksek saptanmıştır (17). Göçmen gebe kadınlarda düşük doğum ağırlıklı fetus ve erken doğum riskinin artması tüm dünyada karşılaşılabilen bir sağlık sorunudur (18). Bir başka çalışmada mülteci grubundaki gebelerin, Türkiye vatandaşı gebelere göre anlamlı olarak daha genç ve daha düşük gebelik haftaları, düşük doğum ağırlıkları ve gebelik öncesi VKİ değerlerine sahip oldukları bulunmuştur (11). Ortalama doğum ağırlığı Suriyeli mülteci gebelerde anlamlı olarak daha düşük olma nedenleri rutin doğum öncesi bakım eksikliği, yetersiz beslenme, düşük sosyoekonomik düzey ve dil sorunları olabilir. Birinci basamak sağlık hizmetlerinde özellikle göçmen sağlığı açısından gebelerin düzenli antenatal takiplerinin ve takviye tedavilerin (demir, D vitamini, multivitamin) yaygınlaştırılması planlanabilir.

Suriyeli hasta grubunda parite daha yüksek bulunmuştur.Suriyeli olguların daha önce yaptığı sezaryenle doğum sayısı, Türkiye vatandaşı gebelerden istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır.Çalışmamızda doğum şekilleri incelendiğinde göçmen popülasyonda normal doğum oranı daha yüksek bulunmuştur. Sezaryen doğum oranları Türkiye vatandaşı olan grupta daha yükseksaptanmıştır ancak sezaryen endikasyonları açısından iki grup arasında fark saptanmamıştır. Sezaryen endikasyonları Tablo 1 ve Şekil 1'de gösterilmiştir. Kliniğimizde normal doğumu destekleyen sağlık uygulamalarını benimsediğimiz için sonuçlarımızın daha olumlu olduğunu düşünmekteyiz. Bu durum ayrıca ülkemizde normal doğum oranlarını arttırma politikalarının olumlu sonuç verdiğini göstermektedir.

2016 yılında yayınlanan bir meta analizde otuz üç çalışma analiz edilmiş ve Türkiye vatandaşlarında genel sezaryen oranları çalışmaların %30'unda daha yüksek, %17'sinde daha düşük ve %30'unda karışık bulunmuştur. Aynı çalışmada Sahra Altı Afrikalı göçmenlerin sezaryen riski daha yüksek iken Doğu Avrupalı göçmenlerin sezaryen riskleri daha düşük bulunmuştur. Göçmen gruplarda sezaryen oranlarındaki artışın altında yatan nedenler kötü yaşam koşulları, kültür ve dil farklılıklarından kaynaklanıyor olabilir (17-19).

Mülteci annelerde sezaryen oranı %30,2 ile Türk annelerden (%39,4) daha düşüktür. Mültecilerde birincil sezaryen oranı daha düşük olmasına rağmen, mükerrer sezaryen oranı benzerdi. Lübnan'daki 6366 Suriyeli mülteci içeren bir seride %35'lik bir sezaryen oranı bildirmiştir. Huster tarafından yapılan başka bir çalışmada oran bizim çalışmamızdakinden daha yüksekti (%57'ye karşı %44) ve Suriye'deki sezaryen oranı savaştan önce %12-15 olarak bildirildi (20). Türkiye'de yapılan son çalışmalarda Suriyeli mültecilerin ve Türk vatandaşlarının sezaryen oranları bizim çalışmamıza benzer şekilde %32,3'e karşı %43,1 ve %30'a karşı %44 olarak bildirilmiştir (20-23). Türkiye'de sezaryen oranının zaman içinde düştüğü unutulmamalıdır. Mülteci doğum öncesi değerlendirme oranı düşük görünmektedir, ancak çoğu mülteci Türkçe veya İngilizce konuşamadığı için çoğu zaman sağlık hizmeti sağlayıcıları doğum öncesi öykü alamamaktadır, buna bağlı olarak doğum oranları, antenatal takip sayıları farklılıklar gösterebilmektedir (24).

Türkiye'deki tüm Suriyeli mültecilerin %47,3'ü kadınlardan oluşmakta olup, bunların %67'si 18-45 yaş aralığındadır (3). Gebelik sayısının artmasını ve dolayısıyla gebelik komplikasyonlarının artmasını beklemek makul olacaktır. Türkiye devleti, mültecilerin mülteci kampları dışında sağlık hizmetlerine erişimlerini sağlamak için Suriyeli mültecilerin sağlık giderlerinin devlet tarafından karşılandığı bir sistem geliştirmiştir. Bu sistem kapsamında gebe mültecilere Sağlık Bakanlığı'nın rutin gebelik takip rehberi doğrultusunda ücretsiz doğum öncesi takip yapılmakta, vitamin ve demir takviyesi verilmektedir (25-26). Mevcut sonuçlar ışığında sağlık sistemindeki göçmen destek uygulamaları olumlu sonuç vermektedir.

SONUÇ

Göçmen sorunu global olarak değerlendirilmesi gereken bir sorundur. Sadece Türkiye ve Suriye değil tüm dünya savaşlar,iç karışıklıklar, iklim krizleri nedeniyle gelecekte de kitlesel göçlerle karşı karşıya kalacaktır. Sağlık hizmeti sağlayıcılarının da göçmen sağlığı için değerlendirmeler yapması ve iyileştirme çözümlerini bulması, devletlerin de göçmen sağlığı ile ilgili politikalar üretmesi gerekmektedir. Çalışmamızdan elde ettiğimiz veriler sonucunda Türkiye devletinin göçmen sağlığı politikaları olumlu sonuç verdiği görülmektedir. İklim değişiklikleri, savaşlar, ekonomik sorunlar gibi nedenlerle oluşabilen göçler sonucunda göçmenlere göç ettikleri yerin sosyokültürel yapısı göz önüne alınarak koruyucu ve tamamlayıcı sağlık hizmeti verilmelidir. Bu sağlık hizmeti hem göç eden halkın hem göç alan halkın tamamlayıcı, bütünleyici bir şekilde; güvenle, sağlıkla yaşamalarına imkan verir.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Is the use of first-trimester systemic inflammation markers predictive in fetal growth restriction?

Birinci trimester sistemik inflamasyon belirteçleri fetal büyüme kısıtlılığı prediksiyonunda kullanılabilir mi?

Zahid AGAOGLU[1], Atakan TANACAN[1,2], Ramazan DENIZLI[3], Bedri SAKCAK[4], Nihat FARISOGULLARI[5], Murat HAKSEVER[1], Özgür KARA[1], Dilek SAHIN[1,2]

[1]Division of Perinatology, Department of Obstetrics and Gynecology, Ministry of Health, Ankara City Hospital, Ankara, Türkiye
[2]University of Health Sciences, Ankara City Hospital, Ankara, Türkiye
[3]Hatay Training and Research Hospital, Hatay, Türkiye
[4]Elazig Fethi Sekin City Hospital, Elazig, Türkiye
[5]Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye

ABSTRACT

Aim: To predict fetal growth restriction (FGR) and its effect on prognosis according to changes in systemic inflammation indexes, such as the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic inflammation response index (SIRI).

Materials and Methods: The study group consisted of 200 women with singleton pregnancies diagnosed with FGR, and the control group comprised 280 obstetrically and demographically matched healthy pregnant women. The NLR, SII, and SIRI were compared between the groups according to the first-trimester complete blood count results.

Results: When the groups were compared in terms of systemic inflammation indexes, the NLR, SII, and SIRI were found to be statistically lower in the FGR group ($p<0.001$, $p=0.01$, and $p=0.03$, respectively).

Conclusion: We found that the NLR, SII, and SIRI were lower in pregnant women with FGR compared to the control group, according to the first-trimester complete blood count analysis.

Keywords: fetal growth restriction, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index

ÖZ

Amaç: Çalışmanın amacı, nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik inflamasyon yanıt indeksi (SIRI) gibi sistemik inflamasyon indekslerindeki değişikliklerin, fetal büyüme kısıtlılığı (FGR) ve prognoz üzerindeki etkisini tahmin etmekti.

Gereç ve Yöntemler: Çalışma grubu FGR tanısı almış tekil gebeliği olan 200 kadın, kontrol grubu ise obstetrik ve demografik olarak eşleştirilmiş 280 sağlıklı gebe kadın oluşturmaktaydı. Birinci trimester tam kan sayımı sonuçlarına göre gruplar arasında NLR, SII ve SIRI karşılaştırıldı.

Bulgular: Gruplar sistemik inflamasyon indeksleri açısından karşılaştırıldığında, NLR, SII ve SIRI'nin FGR grubunda istatistiksel olarak daha düşük olduğu bulundu (sırasıyla $p<0,001$, $p=0,01$ ve $p=0,03$).

Sonuç: FGR'li gebelerde birinci trimester tam kan sayımı analizine göre NLR, SII ve SIRI'nin kontrol grubuna göre daha düşük bulunmuştur.

Anahtar Kelimeler: fetal büyüme kısıtlılığı, nötrofil-lenfosit oranı, sistemik immün-inflamasyon indeksi, sistemik inflamasyon yanıt indeksi

INTRODUCTION

Fetal growth restriction (FGR) is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile according to the week of gestation in a standard population growth curve on an ultrasonographic examination (1). Since FGR is associated with high perinatal morbidity and mortality, early diagnosis and management are extremely important (2). The etiology of FGR includes maternal, fetal, and placental causes (1). Although the use of some ultrasound and biomarkers is recommended to predict pregnant women with FGR in the first trimester, there is not yet any marker that has been introduced into clinical use (3).

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Sorumlu Yazar/Corresponding Author: Zahid AGAOGLU, Department of Obstetrics and Gynecology, Turkish Ministry of Health Ankara City Hospital. Universiteler Mahallesi Bilkent Cad. No: 1 Cankaya/Ankara, Türkiye
E-mail: zahidagaoglu04@hotmail.com

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The first stage of pregnancy begins with the attachment of the embryo to the endometrium, known as implantation. Increased maternal immune responses during implantation may lead to failure in blastocyst-endometrium interactions (4). In the first trimester, neutrophils are located in an area that is involved in the physiological decidual implant reaction, shows high resistance to apoptosis, and expresses fibro/angiogenic factors (5). Immune cells play a fundamental role in successful pregnancy outcomes, and changes in the immune response may lead to complicated pregnancies (6). Disruptions in the implantation process can cause the abnormal development of the spiral arteries, which may lead to preeclampsia or FGR (7).

Systemic inflammation is a response of the immune system to stimuli such as infection, stress, and physical trauma (8). Inflammation markers can be used to detect the presence of systemic inflammation and as early markers of potential disease (9). Among the systemic inflammation markers that can be simply calculated using a complete blood count analysis are the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic inflammation response index (SIRI).

The primary aim of this study was to predict FGR based on changes in systemic inflammation markers, namely the NLR, SII, and SIRI. Second, we divided the FGR cases into two groups according to the onset of disease [early-onset (EO) FGR and late-onset (LO) FGR] and compared the systemic inflammation markers between these subgroups (10). Lastly, we compared the first-trimester systemic inflammation markers of the FGR cases with and without neonatal intensive care unit (NICU) requirements.

MATERIAL AND METHOD

This retrospective, case-control study was conducted at Perinatology Department of Ankara City Hospital from January 1, 2020, through September 1, 2022, in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Medical Research Ethics Unit of the hospital (E2-22-2848).

Study design

Since this study aimed to evaluate pregnant women with a diagnosis of FGR, we screened all births with FGR that occurred during the study period and included cases eligible for the study. Incomplete digital or paper records, incomplete laboratory analyses, and underage patients were excluded from the study. Cases presenting with infection or inflammatory disease were excluded from the study in order to avoid confounding factors. In addition, pregnant women who received corticosteroid and anti-inflammatory treatment, which could affect their inflammation scores during the sampling period, were excluded from the study. Other exclusion criteria were the presence of multiple pregnancies, imminent abortion, autoimmune diseases, diabetes, chronic hypertension, or major anomalies and chromosomal abnormalities in the fetus during the following gestational weeks.

The gestational ages of all pregnant women were confirmed by first-trimester ultrasound recordings. The ultrasonographic evaluation was performed using a Voluson E8 (GE Medical Systems, Solingen, NRW, Germany) device with a GE C2-9-D probe. Fetal biometry was evaluated by measuring the biparietal diameter, head circumference, abdominal circumference, and femur length. EFW and percentile values were calculated according to the formula of Hadlock et al. (11). The diagnosis of FGR was made using the guidelines of the American College of Obstetricians and Gynecologists (1). The cases diagnosed with FGR before 32 weeks of gestation were included in the EO-FGR group, and those diagnosed after 32 weeks were included in the LO-FGR group.

The sample consisted of a total of 480 participants, including 200 women with singleton pregnancies diagnosed with FGR and 280 obstetrically and demographically matched healthy pregnant women. Systemic inflammation markers were calculated using the results of complete blood count analysis performed during the first trimester as follows (12):

NLR = absolute neutrophil count / absolute lymphocyte count

SII = (absolute neutrophil count × absolute platelet count) / absolute lymphocyte count

SIRI = (absolute neutrophil count × absolute monocyte count) / absolute lymphocyte count

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v. 25, IBM, SPSS for Windows, NY: IBM Corp.). Visual and analytical methods (Kolmogorov-Smirnov test) were used to determine whether the variables were normally distributed. Descriptive statistics were presented as median and interquartile range values for non-normally distributed variables. Since continuous variables were not normally distributed, the Mann-Whitney U-test was conducted to compare median values between groups. Using the receiver operating characteristic (ROC) curve method, the predictive performance of inflammation markers for FGR risk was evaluated by calculating the area under the curve (AUC) values and their associated significance values. The optimal cut-off values of inflammation markers were obtained using Youden's index. A p value of <0.05 was considered statistically significant in comparisons between groups.

RESULTS

The study included a total of 480 pregnant women, of whom 200 were diagnosed with FGR and 280 had uncomplicated pregnancies. The demographic and perinatal characteristics and systemic inflammation markers of all participants are presented in Table 1. The cases in both groups were found to be similar in terms of maternal age, body mass index, gravida, and parity (p>0.05). Week of birth, fetal birth weight, first-minute APGAR score, and fifth-minute APGAR score were found to be lower in the FGR group (p<0.001). When the groups were compared in terms of systemic inflammation markers, the NLR, SII, and SIRI were statistically significantly lower in the FGR group (p<0.001, p=0.01, and p=0.03, respectively).

A ROC analysis was performed to evaluate the predictive power of systemic inflammation markers for FGR cases (Table 2). When the cut-off value for the NLR was taken as 3.31, it had 39% specificity and 43% sensitivity for this prediction [AUC: 0.384, 95% confidence interval (CI): 0.334-0.435, p<0.001). At a cut-off value of 806, the SII had a specificity of 40% and a sensitivity of 45% (AUC: 0.413, 95% CI: 0.362-0.465, p = 0.01). Lastly, the specificity and sensitivity values of the SIRI were found to be 45% and 49%, respectively, at a cut-off value of 1.47 (AUC: 0.442, 95% CI: 0.390-0.494, p=0.03).

The comparison of the EO-FGR and LO-FGR cases according to systemic inflammation markers is presented in Table 3. The two groups were statistically similar in terms of the NLR, SII, and SIRI (p=0.760, p=0.546, and p=0.737, respectively).

Table 1. Comparison of the demographic, perinatal, and systemic inflammation markers of the study and control groups

	FGR (n = 200)		Control (n = 280)		
	Median	IQR	Median	IQR	P
Maternal age (years)	28	7	28	7	0.612
BMI (kg/m²)	27.29	7.21	26.22	5.88	0.199
Gravidity	2	2	2	2	0.509
Parity	1	1	1	1.75	0.374
Gestational age at birth (weeks)	37	1	39	1	**<0.001**
Fetal birth weight (grams)	2350	506	3150	510	**<0.001**
First-minute APGAR score	7	1	7	1	**<0.001**
Fifth-minute APGAR score	9	1	9	0	**<0.001**
NLR	3.10	1.63	3.63	1.83	**<0.001**
SII	787	553	907	568	**0.01**
SIRI	1.44	0.96	1.58	1	**0.03**

Mann-Whitney U test, FGR: Fetal growth restriction, IQR: Interquartile range, BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index
p<0.05 was considered statistically significant.

Table 2. Results of the receiver operating characteristic analysis on the ability of systemic inflammation markers to predict FGR cases

	Cut-off	AUC	P	95% CI	Sensitivity	Specificity
NLR	3.31	0.384	<0.001	0.334-0.435	43%	39%
SII	806	0.413	0.01	0.362-0.465	45%	40%
SIRI	1.47	0.442	0.03	0.390-0.494	49%	45%

FGR: Fetal growth restriction, AUC: Area under the curve, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index
p<0.05 was considered statistically significant.

Table 3. Comparison of systemic inflammation markers in groups of early onset-FGR and late onset-FGR

	Early-onset FGR (n = 34)		Late-onset FGR (n = 166)		
	Median	IQR	Median	IQR	P
NLR	3.19	1.32	3.09	1.71	0.760
SII	838	398	773	561	0.546
SIRI	1.45	0.97	1.45	0.94	0.737

Mann-Whitney U test, FGR: Fetal growth restriction, NLR: Neutrophil lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, IQR: Interquartile range
p<0.05 was considered statistically significant.

Table 4. Comparison of systemic inflammation markers according to NICU requirements

	Admission to NICU				
	Present (n = 51)		Absent (n = 149)		
	Median	IQR	Median	IQR	P
NLR	3.09	1.72	3.15	1.53	0.897
SII	771	693	778	534	0.822
SIRI	1.32	1.39	1.47	0.89	0.717

Mann-Whitney U test, NICU: Neonatal intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, IQR: Interquartile range
p<0.05 was considered statistically significant.

Table 4 presents the results of the comparison of systemic inflammation markers according to NICU requirements among the FGR cases. The NLR, SII, and SIRI values were statistically similar between the patients with and without NICU requirements (p = 0.897, p = 0.822, and p = 0.717, respectively).

DISCUSSION

This retrospective case-control study found that systemic inflammation markers, namely the NLR, SII, and SIRI, which can be simply calculated using the first-trimester complete blood count analysis, were lower in pregnant women with FGR than in the control group. On the other hand, these markers were statistically similar when compared between the EO-FGR and LO-FGR cases and between the FGR cases with and without NICU requirements.

The maternal immune system undergoes major adaptations during pregnancy to protect both the mother and the fetus from pathogenic damage, while maintaining fetal allograft tolerance (13). The interface between the maternal decidua and trophoblasts is a dynamic microenvironment in which interactions between cells of fetal and maternal origin occur (14). Maternal immune cells accumulate in this area in response to foreign tissues of the fetus. These immune cells play an important role in decidualization, trophoblast invasion, and remodeling mechanisms, forming the basis of a healthy pregnancy, and their imbalance can lead to pregnancy complications (6).

Systemic inflammation indexes have frequently been the subject of investigation for many researchers. It has been suggested that these indexes can predict the prognosis of some cancer types and can be used to indicate exacerbations in autoimmune diseases (15-17). In recent years, researchers have reported that the use of these indexes may be beneficial in complicated pregnancies, such as preeclampsia, FGR, and preterm delivery (9, 18-20).

In a study in which complete blood count analyses were undertaken during the first trimester of pregnancy to evaluate the prediction of preeclampsia, the NLR and the platelet-to-lymphocyte ratio (PLR) were found to be higher in the preeclampsia group, and the authors suggested that increased NLR and PLR might be a risk factor for this condition (21). In another study, the NLR and SII determined during the first trimester could predict miscarriage, with these markers being higher in women who experienced pregnancy loss (22). Another study reported that the NLR and SII were higher in severe cases of hyperemesis gravidarum (HEG) and claimed that systemic inflammation markers could be used to predict HEG severity (23).

Harita et al. examined the leukocyte and neutrophil counts of pregnant women diagnosed with FGR based on the results of a complete blood count analysis performed in the first or third trimester and compared these values to those of a control group. The authors found that both groups had similar results in the first trimester, but the FGR group had higher leukocyte and neutrophil counts in the third trimester, suggesting that increased maternal inflammation might be a factor in the development of FGR (24). In another study examining the relationship between the NLR and fetal birth weight, no such relationship was observed (25). Levy et al. reported that women who gave birth to small-for-gestational-age neonates had higher NLR values than controls according to the first-trimester complete blood count results (20). In contrast, our results revealed lower inflammation markers in pregnant women with FGR. In a study conducted in China to determine the reference ranges of systemic inflammation markers, such as the SII and NLR, in healthy pregnant women and non-pregnant women, the NLR and SII values of the former were found to be approximately twice those of the latter. Furthermore, the median NLR value was 3.53 (1.76-6.76), and the SII median value was 754 (302-1,603) among pregnant women during their first trimester (26). These results show that systemic inflammation markers evaluated in the first trimester can vary widely. In addition, in a study on neutrophil heterogeneity in inflammation, it was demonstrated that neutrophils could exhibit

different functions and phenotypes in the presence of a disease (27). In a healthy pregnancy series, the balance of neutrophils of different phenotypes was reported to be more important than the quantitative number of neutrophils (6). Our study, conducted with the highest number of pregnant women diagnosed with FGR in the literature, suggests that the contribution of systemic inflammation markers to the clinical evaluation of FGR may be limited.

This study has some limitations that should be discussed. First, since the study was planned at a single center, our sample size was small. Therefore, multicenter, randomized, controlled studies with larger samples are needed. Second, only one blood sample was taken from the participants. Further studies can be designed to collect repeated blood samples to report changes in systemic inflammation markers. The strength of our study is that it is the largest study in the literature evaluating pregnant women with a diagnosis of FGR.

We found that the NLR, SII, and SIRI were lower in pregnant women with FGR compared to the control group, according to first-trimester complete blood count results. However, the NLR, SII, and SIRI did not statistically significantly differ according to the onset of FGR or NICU requirements.

Conflict of interest statement
None

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Author contribution
ZA: methodology, data collection, writing, editing, AT: technical assistance, data collection, correction, analysis, RD: methodology, writing, editing, analysis, BS: technical assistance, data collection, correction, analysis, NF: technical assistance, writing, editing, analysis, MH: technical assistance, writing, editing, analysis, OK: technical assistance, data collection, correction, analysis, DS: methodology, design, correction, analysis

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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İlk trimester tiroid stimulan hormon değerlerine göre maternal, fetal ve perinatal sonuçlar: Retrospektif bir kohort çalışması

Maternal, fetal and perinatal outcome according to first trimester TSH values: a retrospective cohort study

Kamran ALİYEV[1], Fatih AKKUŞ[2], Şükran DOĞRU[2], Huriye EZVECİ[2], Kazım GEZGİNÇ[1]

[1]Necmettin Erbakan Üniversitesi Tıp Fakültesi Hastanesi, Kadın Hastalıkları ve Doğum Ana Bilim Dalı, Konya, Türkiye
[2]Necmettin Erbakan Üniversitesi Tıp Fakültesi Hastanesi, Kadın Hastalıkları ve Doğum Ana Bilim Dalı Perinatoloji, Konya, Türkiye

ÖZ

Amaç: Çalışmanın amacı ilk trimesterde tiroid stimulan hormon (TSH) seviyelerinin subklinik grupta maternal, fetal ve perinatal sonuçlara etkisini araştırmaktır.

Gereç ve Yöntemler: Retrospektif çalışmada Kasım 2020 - Kasım 2021 tarihleri arasında NEÜ Meram Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum kliniğinde doğumu gerçekleşen 18-45 yaş arası 745 tekil gebe değerlendirildi. TSH değerine aynı klinikte ve gebeliğin ilk trimesterinde bakıldı. Çoğul gebelikler, çalışmaya dahil edilmedi. 175 hasta çeşitli ek hastalıklar sebebi ile çalışma dışı tutuldu. Hastalar TSH değerine göre subklinik hipertiroidi, ötiroidi ve subklinik hipotiroidi olmak üzere üç gruba ayrıldı. Çalışma grupları arasında maternal, fetal ve perinatal sonuçları karşılaştırıldı.

Bulgular: Subklinik hipotiroidi grubunda maternal anemi, yenidoğan yoğun bakım ünitesi (YYBÜ) ihtiyacı, preterm erken membran rüptürü (PPROM), gestasyonel hipertansiyon, fetal gelişim kısıtlılığı (FGR) oranları anlamlı olarak daha fazla görüldü ($p<0,05$). Subklinik hipertiroidili gebelerde ise maternal anemi oranları ötiroid gebelere göre anlamlı derecede fazlaydı ($p<0,05$).

Sonuç: İlk trimesterde bakılan TSH değerinin maternal sonuçlar üzerine etkileri olduğu görülmektedir. TSH düzeylerinin fetal etkileri de olabileceği düşünülmektedir. Ancak uzun dönem fetal etkileri açısından iyi tasarlanmış çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Perinatal sonuç, Obstetrik sonuç, TSH değeri, İlk trimester

ABSTRACT

Aim: The aim of the study was to investigate the effect of thyroid stimulating hormone (TSH) levels in the first trimester on maternal, fetal and perinatal outcomes in a subclinical group.

Materials and Methods: In this retrospective study, 745 singleton pregnancies aged 18-45 years who were delivered in the Obstetrics and Gynecology clinic of NEU Meram Medical Faculty Hospital between November 2020 and November 2021 were evaluated. TSH was measured in the same clinic and in the first trimester of pregnancy. Multiple pregnancies were not included in the study. 175 patients were excluded due to various comorbidities. Patients were divided into three groups as subclinical hyperthyroidism, euthyroidism and subclinical hypothyroidism according to TSH values. Maternal, fetal and perinatal outcomes were compared between the study groups.

Results: Maternal anemia, neonatal intensive care unit (NICU) requirement, preterm premature rupture of membranes (PROM), gestational hypertension, fetal growth restriction (FGR) rates were significantly higher in the subclinical hypothyroidism group ($p<0.05$). Maternal anemia rates were significantly higher in pregnant women with subclinical hyperthyroidism compared to euthyroid women ($p<0.05$).

Conclusion: First trimester TSH levels seem to have effects on maternal outcomes. It is thought that TSH levels may also have fetal effects. However, well-designed studies are needed in terms of long-term fetal effects.

Keywords: Perinatal outcome, Obstetric outcome, TSH value, First trimester

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Sorumlu Yazar/Corresponding Author: Kamran ALİYEV, Necmettin Erbakan Üniversitesi Tıp Fakültesi Hastanesi, Kadın Hastalıkları ve Doğum Ana Bilim Dalı, Konya, Türkiye
E-mail: opdrkaliyev@gmail.com

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GİRİŞ

Gebelik süresince ortaya çıkan immünolojik, metabolik ve hormonal değişikliklerin tiroid bezi üzerinde de önemli etkileri olur. Tiroid hastalıkları üreme çağındaki kadınlarda ikinci sıklıkla izlenen endokrinolojik bozukluktur (1). Bu hastalıkların erken tanımlanıp tedavi edilmesi fetal ve maternal sağlık için oldukça önemlidir. Tiroid hormonu gebelik oluşumu, embriogenez, maturasyon ve normal plasenta gelişimi için gerekli olup 12-14. haftadan itibaren fetüs tarafından salgılanmaya başlar (2, 3).

Gebelerde dört ile sekizinci gebelik haftasından itibaren tiroksin bağlayıcı globülin (TBG) düzeyleri dolaşımda iki kat artar. Tiroid dokusu yeterli serbest tiroid hormonunu dolaşıma vermek için ve human koryonik gonadotropinin (hCG'ın) TSH (tiroid stimulan hormon) reseptörlerinde, TSH benzeri etki göstermesiyle tiroksin (T4) ve triiodotironin (T3) üretimini artırır. Bununla da T4 ve T3 konsantrasyonları gebeliğin ilk yarısında artarak 20. haftada plato çizer ve sonuçta ilk trimesterde TSH seviyeleri düşer. Gebe kadınlar, gebe olmayanlara göre daha düşük serum TSH düzeylerine sahiptirler (4, 5). Gebelik boyunca hamilelerde fizyolojik değişimler nedeniyle American Thyroid Association (ATA) bir kılavuz yayınlayarak gebelik için referans değerler belirlemiştir (5). TSH değeri gebeliğin ilk trimesterinde en yüksek 2,5 mIU/L, ikinci ve üçüncü trimesterinde ise 3,0 mIU/L düzeylerinde olmalıdır. Normal alt sınır ise ilk trimester için 0,1 mIU/L, ikinci ve üçüncü trimesterde ise uygun olarak 0,2 mIU/L ve 0,3 mIU/L olarak belirlenmiştir. Gebe kadınlarda rutin tiroid fonksiyon testlerinin taranması ile ilgili fikir birliği bulunmamaktadır. Türkiye Endokrinoloji ve Metabolizma Derneği (TEMD) gebelik tiroid fonksiyonlarının değerlendirilmesinde TSH bakılmasını önermektedir 6).

Gebelerin 3-4/1000'ü semptomatik (hipotiroidi), 2-3/1000'ü ise subklinik hipotiroidi ile komplike olmaktadır (7) En sık neden ise endemik iyot eksikliği ya da otoantikor pozitif olan Haşimato tiroiditidir. Hipertiroidizm, 1-4/1000 gebelikte rastlanır (7). Bunun gebelerde en sık nedeni ise Graves hastalığıdır (5).

Hipotiroidizm maternal ve fetal çeşitli komplikasyonlara neden olmaktadır. Hipotiroidizm; abortus, gestasyonel hipertansiyon, anemi, plasenta dekolmanı ve postpartum hemoraji risklerini artırmaktadır (8). Çocuk planlayan kadınlarda TSH'ın 2,5 mU/L'nin altında hatta mümkünse 1,2 mU/L 'den az olması olması istenmektedir (9). Olumsuz olaylar için açık kanıtların olduğu klinik (belirgin) hipotiroidi ile karşılaştırıldığında, subklinik hipotiroidinin gebelik üzerindeki tam etkisi belirsizdir (4, 10). Bu çalışmada ilk trimester TSH değerlerinin perinatal ve obstetrik sonuçlara etkisini araştırmayı hedefledik.

GEREÇ VE YÖNTEMLER

Retrospektif planlanmış olan çalışmaya Kasım 2020 - Kasım 2021 tarihleri arasında NEÜ Meram Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde doğum yapan gebeler alındı. Gebeliğin ilk trimesterinde TSH değerine aynı klinikte bakılmış, 18-45 yaş arası 745 tekil gebe değerlendirildi. Çoğul gebelikler, sonuçları yanıltıcı olabileceğinden çalışmaya dahil edilmedi. 175 hasta çeşitli ek hastalıklar sebebi ile çalışma dışı tutuldu. Bunlara ek olarak viabilite sınırına (24 hafta ve/veya 500 gr) ulaşmamış gebelikler (n=9) de kapsam dışı tutuldu. Çalışma dışında tutulan gebeleri sınıflayacak olursak tiroid fonksiyon bozukluğu olan hastalar (sT4 değerleri referans 0.93-1.7 ng/dL dışı olanlar, otoantikorları pozitif olanlar, TSH >10 mU/L olanlar), kalp hastalıkları (hipertansiyon, mitral darlık, aort stenozu), hematolojik hastalıklar (anemiler, talasemiler, trombositopeniler, Von Willibrand Hastalığı) diğer sistemik hastalıklar (Romatoid Artrit, Nefrotik Sendrom, Sistemik Lupus Eritematozus) gibi ayıra biliriz.

Hastalar TSH değerlerine göre üç gruba ayrıldı. Birinci grup TSH<0.1 mU/L (n=18, %3.2) olan subklinik hipertiroidi, ikinci grup TSH= 0.1-2.5 mU/L (n=431, %75.6) olan ötiroid ve üçüncü grup TSH>2.5 mU/L (n=121, %21.2) olan subklinik hipotiroidi gebeler şeklinde ayrıldı. Kliniğimizde, ilk trimesterde TSH düzeyleri 0,1 mU/L'nin altında ve 2,5 mU/L'nin üzerinde olan gebeler serum tiroksin (sT4) ve tiroid otoantikorları, yani anti-tiroidperoksidaz (anti-TPO) ve anti-tiroglobulin antikorları açısından değerlendirildi. Referans aralık olan 0,93-1,7 ng/dL dışında sT4 düzeyleri olan ve otoantikorları pozitif olan hastalar çalışmadan çıkarılmıştır. Bu çalışmada, maksimum TSH sınırını 5 olarak belirledik ve 570 hastadan oluşan bir kohortta gebeliğin ilk üç ayında (6-12 hafta) TSH düzeylerini değerlendirdik. Subklinik hipertiroid, ötiroid ve subklinik hipotiroid gruplarına yalnızca önemli tiroid hastalığı, diabetes mellitus, kalp hastalığı, hematolojik ve sistemik hastalıkları olmayan ve sigara veya alkol kullanmayan hastalar dahil edildi. Gruplar maternal yaş, gravida, parite, doğan bebeklerin cinsiyetine bakılarak doğum ağırlıkları, doğum zamanı (hafta), ilk (6-12. haftasında TSH değeri bakılan zaman) maternal hemoglobin değeri, anemi oranları, plasental invazyon bozuklukları, preeklampsi, gestasyonel hipertansiyon (GHT), fetal gelişim kısıtlılığı (FGK), preterm erken membran rüptürü (PPROM), oligohidramnios, polihidramnios, dekolman, yenidoğan ilk (1) dakika ve 5. dakika APGAR'ı, yenidoğan yoğun bakım ünitesi ihtiyacı (YYBÜ) , fetal anomali, ölü doğum, anne ve bebek ölümü olması gibi perinatal ve obstetrik açıdan karşılaştırıldı. Tiroid fonksiyon testi sonuçları, yaş, gebelik haftası, gebelik öyküsü, eşlik eden hastalıklar, ameliyat sonrası kan değerleri ve klinik özellikler dahil olmak üzere tüm hasta verileri tıbbi kayıtlardan ve hastanenin elektronik arşiv veri tabanından (ENLIL) elde edilmiştir.

Necmettin Erbakan Üniversitesi (NEÜ) Etik Kurulu ve Sağlık Bakanlığı'ndan gerekli tüm onaylar alınmıştır.

Çalışma, bebekleri doğum ağırlıklarına göre üç gruba ayırmıştır: 2500 gramın altı, 2500-4000 gram arası ve 4000 gramın üstü. Doğum ağırlıkları daha sonra tiroid uyarıcı hormon (TSH) seviyelerine göre karşılaştırıldı. Doğum ağırlığı 2500 gramın altında olan grup düşük doğum ağırlığı grubu olarak sınıflandırılmıştır. Preterm eylem 37. gebelik haftasından önce doğum olarak tanımlanmıştır. Preeklampsi ve gestasyonel hipertansiyon AGOC 2013 kılavuz kriterlerine göre tanımlanmıştır. Anemi, periferik kanda hemoglobin değerinin 11 g/dL'nin altında olması olarak tanımlanmıştır. Fetal büyüme kısıtlılığı (FGR) AGOC 2017 kılavuzuna uygun olarak tahmini ağırlığı gebelik yaşına göre 10. persentilin altında olan fetüsler olarak tanımlanmıştır. Plasental abrupsiyon, plasentanın doğumdan önce uterustan ayrılması olarak tanımlanmıştır. APGAR skorunun 7'nin altında olması düşük APGAR skoru olarak kabul edilmiştir.

İstatistik

Çalışmamızda istatiksel analiz için toplanan tüm veriler "IBM SPSS Statistics 20" ile analiz edildi. Tanımlayıcı istatistikde ortalama ve standart sapma verildi. Parametrik dağılım gösteren verilerin çoklu grup karşılaştırması için tek yönlü varyans analizi (ONE WAY ANOVA) testi kullanıldı. Nonparametrik dağılım gösteren grupların çoklu karşılaştırması için Kruskal-Wallis testi yapıldı. Posthoc değerlendirme için Tamhane's T2 düzeltmesi uygulandı. Nominal değişkenlerin karşılaştırmasında Ki-kare testi kullanıldı. İstatistik anlamlılık düzey ise p<0,05 kabul edildi.

BULGULAR

Tablo 1'de gösterildiği gibi, çalışma popülasyonu 570 hastadan oluşmakta olup, Grup 1 subklinik hipertiroidi sergileyen 18 kişiyi (%3,2), Grup 2 ötiroid olarak sınıflandırılan 431 katılımcıyı (%75,6) ve Grup 3 subklinik hipotiroidi sergileyen 121 kişiyi (%21,2) kapsamaktadır.

On sekiz hastadan oluşan subklinik hipertiroidi grubunda ortalama yaş 29,05±4,07'dir. Ötiroidi grubunda ise 431 hastayı kapsayan ortalama yaş 29,75 ± 5,86'dır. Subklinik hipotiroidi grubundaki 121 hastanın yaş ortalaması 29,07± 5,97 idi. İstatistiksel analiz, gruplar arasında yaş açısından anlamlı bir fark olmadığını göstermiştir (p= .491). Benzer şekilde, gravidite (p= .626) ve parite (p= .107) açısından da gruplar arasında anlamlı bir fark gözlenmemiştir. Subklinik hipertiroidi grubunun ortalama graviditesi 3,05±1,39, ötiroidi grubunun ortalama graviditesi 2,75±1,54 ve subklinik hipotiroidi grubunun ortalama graviditesi 2,67±1,67 idi. Buna karşılık gelen medyan parite değerleri sırasıyla 1(0-3), 1(0-5) ve 1(0-5) idi. TSH düzeyleri açısından gruplar arasında anlamlı bir fark gözlenmiştir (p= .001). Subklinik hipertiroidi grubunun ortanca TSH düzeyi 0,06 (aralık: 0,008-0,09) mU/L, ötiroidi grubunun ortanca TSH düzeyi 1,36 (aralık: 0,19-2,5) mU/L ve subklinik hipotiroidi grubunun ortanca TSH düzeyi 3,02 (aralık: 2,51-5,0) mU/L idi (Tablo 2.)

Ortalama gebelik haftası gruplar arasında anlamlı farklılık göstermiş (p=0,047), subklinik hipertiroidi grubu ötiroidi (38,12±1,43) ve subklinik hipotiroidi (37,78±1,75) gruplarına kıyasla en uzun ortalama gebelik haftasına (38,47±0,89) sahip olmuştur.

Tablo 1. Çalışmaya dahil edilen hastalar, sayı, yüzdesi, grup tanımlanması

Gruplar	TSH (mU/L)	Klinik tanım	Hasta sayı (%)
Grup 1	< 0,1	Subklinik hipertiroid	18 (3,2%)
Grup 2	0,1-2,5	Ötiroid	431 (75,6%)
Grup 3	> 2,5	Subklinik hipotiroid	121 (21,2%)

TSH - Tiroid stimulan hormon

Tablo 2. Çalışmaya dahil edilen hastaların TSH, gebelik haftası, gravida ve parite dağılımı *(TSH- Tiroid stimulan hormon , veriler ortalama±SD sunulmuştur* **,** *Parametrik dağılım gösteren verilerin çoklu grup karşılaştırması için tek yönlü varyans analizi,* Nonparametrik *dağılım gösteren grupların çoklu karşılaştırması için Kruskal-Wallis testi yapıldı, Nominal değişkenlerin karşılaştırmasında Ki-kare testi kullanıldı.)*

Parametreler	Subklinik hipertiroidi (n=18)	Ötiroidi (n=431)	Subklinik hipotiroidi (n=121)	P
Hasta yaşı	29,05 ± 4,07	29,75 ± 5,86	29,07 ± 5,97	,491
Gravida	3,05 ± 1,39	2,75 ± 1,54	2,67 ± 1,67	,626
Parite	1(0-3)	1(0-5)	1(0-5)	,107
TSH değeri	0,06 (0,008-0,09)	1,36 (0,19-2,5)	3,02 (2,51-5,0)	**,001***

* : Tamhane ile Posthoc test : Subklinik hipertiroidi grup ve subklinik hipotiroidi grup (p=.001), subklinik hipertiroidi grup ve ötiroidi grup (p=.001), ötiroidi ve subklinikal hipotiroidi (p=.001)

TSH grupları arasında hastanede yatış süresi (p=0,129), plasenta invazyon bozukluğu (p=0,791), preeklampsi (p= 0,846) ve dekolman plasenta (p=0,846) açısından anlamlı bir fark gözlenmemiştir. Gestasyonel hipertansiyon prevalansı gruplar arasında anlamlı farklılık göstermiş (p=0,044), subklinik hipertiroidi grubunda hiç vaka görülmezken, ötiroidi grubunun %1,2'sinde ve subklinik hipotiroidi grubunun %5,0'ında gestasyonel hipertansiyon görülmüştür.

Gestasyonel diabetes mellitus (GDM) prevalansı gruplar arasında bazı farklılıklar göstermekle birlikte, fark istatistiksel olarak anlamlı değildi (p=0,111). Subklinik hipertiroidi grubunda GDM prevalansı (%11,1) ötiroidi grubuna (%6,7) ve subklinik hipotiroidi grubuna (%12,4) kıyasla daha yüksekti. TSH grupları arasında preterm erken membran rüptürü (PPROM) görülme sıklığında anlamlı farklılıklar gözlenmiştir (p=0,0001). Subklinik hipotiroidi grubu en yüksek PPROM prevalansına (%17,4) sahipken, bunu subklinik hipertiroidi grubu (%5,6) ve ötiroidi grubu (%4,6) izlemiştir.

Ayrıca, maternal anemi ötiroidi grubuna (%5,8) kıyasla subklinik hipertiroidi (%16,7) ve subklinik hipotiroidi (%16,5) gruplarında daha yaygındı ve bu fark istatistiksel olarak anlamlıydı (p=0,001). (Tablo 3).

Subklinik hipertiroidizm, ötiroidizm ve subklinik hipotiroidizm grupları arasında doğum ağırlığı (p = 0,107) açısından istatistiksel olarak anlamlı bir fark gözlenmemiştir. Ortanca doğum haftası her üç grup için de 38 hafta idi ve ortanca doğum ağırlığı 3210 gram ile 3390 gram arasında değişiyordu. Yenidoğanın genel iyilik halini değerlendiren doğumdaki APGAR skorları gruplar arasında anlamlı bir farklılık göstermedi (p = 0,661). Ortanca APGAR skoru tüm gruplar için 7 olup, aralık 5 ila 8'dir. Fetal büyüme kısıtlaması (FGR) prevalansı TSH grupları arasında anlamlı farklılık göstermiştir (p = 0,009). Subklinik hipotiroidi grubu en yüksek FGR prevalansına (%17,4) sahipken, bunu ötiroidi grubu (%8,1) ve subklinik hipertiroidi grubu (%5,6) izlemiştir.

Tablo 3. Maternal özelliklerin TSH gruplarına göre karşılaştırılması *(veriler ortalama±SD veya n (%)olarak sunulmuştur, Parametrik dağılım gösteren verilerin çoklu grup karşılaştırması için tek yönlü varyans analizi Nonparametrik dağılım gösteren grupların çoklu karşılaştırması için Kruskal-Wallis testi yapıldı, Nominal değişkenlerin karşılaştırmasında Ki-kare testi kullanıldı.))*

Parametreler	Subklinik hipertiroidi (n=18)	Ötiroidi (n=431)	Subklinik hipotiroidi (n=121)	P
Doğum haftası	38,47 ± 0,89	38,12 ± 1,43	37,78 ± 1,75	**,047***
Hospitalizasyon günü	2,67 ± 0,59	2,61 ± 0,75	2,78 ± 1,02	,129
Gestasyonel hipertansiyon	0 (0,0%) [a,b]	5 (1,2%) [a]	6 (5,0%) [b]	**,044¥**
Preeklampsi	1 (5,6%)	26 (6,0%)	9 (7,4%)	,846
Plasental invazyon bozukluğu	0 (0,0%)	9 (2,1%)	3 (2,5%)	,791
Gestasyonel diabetes mellitus	2 (11,1%)	29 (6,7%)	15 (12,4%)	,111
PPROM	1 (5,6%) [a,b]	20 (4,6%) [a]	21 (17,4%) [b]	**,0001¥**
Dekolman plasenta	0 (0,0%)	2 (0,5%)	1 (0,8%)	,846*
Matenal Anemi	3 (16,7%) [a,b]	25 (5,8%) [a]	20 (16,5%) [b]	**,001¥**

PPROM- preterm erken membraan rüptürü
*: Tamhane ile posthoc test: Subklinik hipertiroidi ve Subklinik hipotiroidi (p=.039)
¥:: D Farklı harfler istatistiksel olarak anlamlı bir farkı gösterir

Tablo 4. Fetal ve perinatal özelliklerin TSH gruplarına göre karşılaştırılması *(veriler ortalama±SD veya n (%)olarak sunulmuştur, Nonparametrik dağılım gösteren grupların çoklu karşılaştırması için Kruskal-Wallis testi yapıldı, Nominal değişkenlerin karşılaştırmasında Ki-kare testi kullanıldı.))*

Parametreler		Subklinik hipertiroidi (n=18)	Ötiroidi (n=431)	Subklinik hipotiroidi (n=121)	P
Doğum ağırlığı(gr)		3390 (2290 – 4130)	3210 (1690 – 4600)	3200 (1100 – 4830)	,107
APGAR		7 (5 – 8)	7 (0 – 9)	7 (0 – 9)	,661
Fetal gelişim kısıtlılığı		1 (5,6%) [a,b]	35 (8,1%) [a]	21 (17,4%) [b]	**,009¥**
Bebek cinsi	Kız	4 (22,2%)	212 (49,2%)	60 (49,6%)	,078
	Erkek	14 (77,8%)	219 (50,8%)	61 (50,4%)	
Fetal Anomali		1 (5,6%)	5 (1,2%)	5 (4,1%)	**,**058
İntrauterin gebelik kaybı		0 (0,0%)	0 (0,0%)	2 (1,7%)	,059
YYBÜ ihtiyacı		2 (11,1%) [a,b]	51 (11,8%) [a]	26 (21,5%) [b]	**,024¥**

YYBÜ- Yenidoğan yoğun bakım ünitesi
¥:: D Farklı harfler istatistiksel olarak anlamlı bir farkı gösterir

TSH grupları arasında cinsiyet dağılımı (p = 0,078) ve fetal anomali görülme sıklığı (p = 0,058) açısından anlamlı bir fark gözlenmemiştir. Gruplar arasında cinsiyet dağılımı nispeten benzerdir. Ölü doğum prevalansı anlamlılığa doğru bir eğilim göstermiş (p=0,059), subklinik hipotiroidi grubunda iki vaka (%1,7) görülürken diğer gruplarda vaka görülmemiştir. Ancak, kesin bir ilişki kurmak için daha fazla araştırma yapılması gerekmektedir. Yenidoğan yoğun bakım ünitesine (YYBÜ) kabul oranı TSH grupları arasında anlamlı farklılık göstermiştir (p=0,024). Subklinik hipotiroidi grubu, subklinik hipertiroidi grubu (%11,1) ve ötiroidi grubuna (%11,8) kıyasla daha yüksek YYBÜ'ye kabul oranına (%21,5) sahipti (Tablo 4).

TARTIŞMA

Gebelikte tiroid fonksiyon testlerinin rutin taranması konusu çelişkili olup ortak bir karar bulunmamaktadır. Çalışmamızda Kasım 2020 - Kasım 2021 içerisinde Meram Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Kliniği' nde doğum yapan hastalar değerlendirildi. Subklinik hipertiroidili hastalar 18 hasta; %3.2, ötiroid hastalar 431 hasta; %75,6 ve subklinik hipotiroidili hastalar 121 hasta; %21,2 izlendi. Subklinik hipotiroidili hastaların sayı Türkiye Endokrinoloji ve Metabolizma Derneğinin Kılavuzunda gebe populasyonunun %2-3 olarak gösterilse de bizim çalışmamızda bu sayı ortalamanın üstünde görüldü. Kliniğimizde rutin olarak ilk trimester taramasında TSH değerlerine bakılımaktadır.

American College of Obstetricians and Gynecologists (ACOG), her gebede tiroid hastalığı taramasını önermemekte olup ancak anamnezinde tiroid hastalığı öyküsü veya ilişkili olabilecek semptomlar görüldüğünde tiroid fonksiyonlarının değerlendirilmesini önermektedir. Ancak Türkiye Endokrinoloji ve Metabolizma Derneğinin önerileri de göz önünde bulundurularak, Türkiyenin iyot eksikliği bölgesi olması, tiroid hormon eksikliğinin gebelikte bir çok olumsuz sonuçlara yol açma riskinin var olması ve TSH ölçümlerinin Türkiyede karşılanabilir bir maaliyette olması nedeni ile gebe kalmayı planlayan tüm kadınlarda ve tüm gebelerde başlangıçta TSH ölçümü yapılması önerilmektedir.

TSH 'ın üst limiti hakkında da verilmiş bir kesin karar bulunmamaktadır. Bazı çalışmalar (11-13) TSH ilk trimester üst limitini 2,30 - 2,99 mU/L arasında önerirken, Marhawave ark. ilk trimester TSH seviyelerini 0,6- 5 mU/L arasında olmasını önermektedir (14, 15). Hem American Thyroid Association (ATA) hem de Türkiye Endokrinoloji ve Metabolizma Derneği kılavuzlarında TSH düzeylerinin ilk üçay'da 0,1-2,5 mIU/ml; ikinci üçay'da 0,2-3,0 mIU/ml ve üçüncü üçay'da 0,3-3,0 mIU/ml aralığında olması gerektiği vurgulanmıştır. ATA 2017 yılında yaptığı yeni çalışmalar ışığında önerisini değiştirmiş ve ilk trimester için TSH eşiğini 2,5 yerine 4,0 olarak belirlemiştir. Ama bu çalışmada etnik ve coğrafi olarak endemik iyot eksikliğinin önemini de vurgulamış ve bu değerlerin coğrafi yerleşime göre farklılık göstere bileceğini belirtmiştir. Amerikan Endokrin Derneği de (The American Endocrinology Society, AES), gebelikte ilk üçay'da TSH' nın üst sınırı olarak 2,5 mIU/ml sınırını kabul etmektedir ve ilk üçay' da TSH>2,5 mIU/ml ve ikinci ve üçüncü üçay' da TSH>3,0 mIU/ Ml olması durumunda gebelere tedavi başlanmasını önermektedir. Bizim çalışmada da ilk trimester normal değerler 0.1-2.5 mIU/Ml sınır olarak kabul edildi.

Gebelikte tedavi edilmemiş tiroid fonksiyon bozuklukları istenmeyen fetal sonuçlara neden olmaktadır, bazı çalışmalarda YYBÜ ihtiyacı, fetal ölüm, ilerleyen yıllarda düşük mental zekaya neden olduğu ortaya konmuştur. Bu sebeple TSH değerinin 2,5' in altında tutulması olası maternal ve fetal komplikasyonları azaltmaktadır. Bizim çalışmamızda subklinik hipotiroidili (G3) gebelerin bebekelerinin YYBÜ ihtiyacı 26 bebekte görülüp (%21.5) diğer gruplara göre anlamı oranda fazla görülmüştür (p=0.024). Kabaca ve ark. yaptığı çalışmada yenidoğan yoğun bakım ihtiyacı subklinik hipotiroidik olgularda ötiroid gebelerden yüksek bulundu (p=0,041) (16). Çalışmamızda intrauterin gebeblik kaybı TSH>2,5 mIU/ml olan grupta (G3) 2 (%1.7) gebede görüldü ve bu sayı diğer gruplara göre anlamlı olarak yüksek bulunmadı (p=0.059). Negro ve ark. çalışmalarında gebelik kaybının TSH 2,5-5 mU/L arasındaki grupta istatistiksel olarak anlamlı yüksek bulunmuştur (17). Aker Ş. ve ark. yaptığı çalışmada da intrauterin ölüm sadece 1 vakada (%0.5) olup ve TSH < 2,5 mU/L olan gruptaydı.

Bilindiği üzere hipotiroidizmde metabolik bir yavaşlama görülür. Bu durumdan tüm organ sistemleri etkilenir ve buna bağlı olarak var olan semptom ve bulgular farklı özellikler göstermektedir. Tiroid hormonların eksikliğine bağlı kemik iliği baskılanır. Tiroid hormonları, eritropoietin yoluyla doğrudan ve ya dolaylı olarak eritroid kolonilerinin büyümesini uyarır. Anemi genellikle hipotiroidizmin ilk belirtilerindendir. Hipotiroidizm çok çeşitli anemik hastalıklara neden olabilir (18, 19). Çalışmamızda subklinik hipotiroidi grupta (G3) ve subklinik hiperiroidi (G1) grupta ötiroidi gruba (G2) oranda istatistik anlamlı (p=0.003) olan daha fazla anemili gebe görüldü. Erdoğan M. ve arkadaşlarının yaptığı çalışmada hipotiroidili hastalarda anemi sıklığında artış olduğunu saptamışlardır ve subklinik hipotiroidizmde de anemi sıklığı aşikar hipotiroidizmdeki kadar yüksek saptanmıştır (20). Bakırcı M. ve ark. TSH >2.5 mIU/L olan grupta hemoglobin seviyesini ötiroidi gruba göre daha düşük olduğunu tespit ettiler ve anemi değerlerine göre anlamlı sonuç elde ettiler (21). Rabet-Bensalah K. ve ark. ötroid olan gebe grupta anemi oranı %4,7, hipertiroidi gebe grupta ise %14,6 olarak tespit etmişlerdir (22).

Fetal büyüme ve gelişme için yeterli maternal tiroid hormonu gereklidir. Fetal büyüme ve tiroid hormonları arasındaki ilişki çeşitli mekanizmalarla açıklanabilir. Toplum ortalamasında FGK %3-9 arasında görülüyor. Bizim çalışmamızda da ötiroid ve subklinik hipertiroid grupta toplum ortalamasıyla uyumlu FGK oranları görüldü. TSH>2,5 mIU/L olan grupta toplum ortalamasının üstünde olup 21 hastada (%17.4) FGK izlenip diğer gruplara göre anlamlı fazla sonuçlar görüldü. Forhead ve ark. fetal büyüme ve gelişme ile tiroid hormonları arasında güçlü bir ilişki olduğunu belirlemiştir (23). Ayrıca tiroid hormonlarının büyüme faktörleri ve katekolaminler üzerindeki düzenleyici etkilerine de dikkat çektiler. Büyüme faktörleri ve katekolaminler, fetus için intrauterin anabolik veya katabolik süreçleri indükler. Forhead ve ark. fetüs için katabolik fazı aktive ederek aşırı tiroid hormonu maruziyeti ile fetal gelişme kısıtlaması arasındaki ilişkiyi açıkladı (23). Anselmo ve ark. aşırı tiroid hormonlarına maruz kalan fetüslerde gelişme geriliği oluşabileceğini gösteren bir çalışma sunmuştur (3). Aker ve ark., Herhandez ve ark. yaptıkları çalışma ile TSH değerleriyle FGK arasında herhangi bir ilişki tespit etmemişler (24, 25).

PPROM oranlarına bakıldığında TSH'ın etkisi Günkaya ve ark. çalışmasında artan TSH değerlerinin aşikar hipotiroidi hasta grubunda EMR oranlarını artırdığını, subklinik gruplarda anlamlı görülmediğini ortaya koymuştur (26). Bu çalışmada oligohidramnios, polihidramnios, preeklampsi, preterm doğum olgularıyla TSH arasında anlamlı ilişki bulunmamıştır. İranda 2021'de Nazarpour ve ark. hazırladığı bir derlemede artan TSH değerlerinin PPROM oranlarını artırdığı tespit edilmiştir (27). Benzer şekilde, Korevaar ve ark. çalışmasında da artan TSH değerlerinin PPROM riskinin arttığını bulmuşlardır (28). Kabaca ve ark. yaptığı çalışmada subklinik hipotiroid grupla ötiroid grup arasında PPROM oranlarında anlamlı fark izlenmedi (16). Bizim çalışmamızda da PPROM oranlarına bakıldığında subklinik hipotiroidili gebelerde bu oran istatistik anlamlı olarak daha fazla görülmüştür. PPROM olguları 12 gebede (%2.1) görüldü.

Subklinik hipotiroidinin önemli tarafı, aşikar hipotiroidi gelişmese de ateroskleroz ve kardiyovasküler hastalık için risk oluşturabilmesidir. Bunlar bozulmuş endotel fonksiyonu, arteriyel intimal media kalınlığının artmış olması ve insülin direnci ile açıklanmaktadır. Klinik hipotiroidizim ve subklinik hipotiroidizim hem sistemik hem de renal damarlarda vasküler düz kas kasılmasına neden olur, bu da diyastolik basıncın artmasına, periferik vasküler dirence ve hipotiroidizmde gebede yüksek tansiyonun patofizyolojisi olabilecek doku perfüzyonunun azalmasına yol açar (29, 30). Tiroid disfonksiyonu, tiroksin ve tiroid bağlayıcı globulinlerin artan atılımıyla sonuçlandığından bilinen proteinüri ile ilişkili olabilir. Proteinürinin vücut tarafından telafi edilemeyen tiroid bağlayıcı globulinler ve tiroksin kayıplarına neden olacak kadar şiddetli olduğu nadir vakalar bildirilmiştir (31-33). Bizim yaptığımız çalışmada ilk trimester TSH değerleri ile GHT arasında anlamlı ilişki görülse de, preeklampsi ile istatistik anlamlı sonuçlar saptanmamıştır. Mahadik ve ark. 2020'de yaptığı çalışmada preeklampsili gebeler subklinik hipotiroidizimle ilişkili bulunmuştur (p=0.041) (34). Ashok ve ark. yaptığı çalışmada normal gebelikle karşılaştırıldığında preeklampside ilk trimester ortalama serum TSH seviyeleri, serbest T3 ve T4'te eşlik eden değişiklikler olmaksızın önemli ölçüde yüksek bulundu (35). Kaba ve ark. yaptığı çalışmada TSH değerlerinin gebede yüksek tansiyonla ilişlkisi görülmemiştir (36).

Yapılan çalışmamızda anlamlı sonuçlar elde edilmiştir. Ancak, TSH değerlerinin gebelikteki obstetrik ve perinatal sonuçlar üzerindeki etkilerini daha detaylı bir şekilde inceleyebilmek için daha kapsamlı, geniş ölçekli ve çok merkezli araştırmalara ihtiyaç vardır.

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The utility of albumin-bilirubin score as a prognostic marker in preeclampsia

Albümin-bilirubin skorunun preeklampside prognostik değerinin araştırılması

Osman Onur ÖZKAVAK[1], Dilek ŞAHİN[1,2]

[1]Department of Perinatology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Obstetrics and Gynaecology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye

ABSTRACT

Aims: To evaluate the utility of the albumin bilirubin (ALBI) score as a liver function test and prognostic marker in patients with preeclampsia.

Materials and Methods: A total of 374 patients were enrolled in the study (148 preeclampsia without severe features, 112 preeclampsia with severe features, 114 controls). The study compared clinical and demographic features, laboratory findings and ALBI scores between the three groups. Also, receiver operating curve (ROC) analysis was used for the estimation of the predictive value of the ALBI score for the severity of preeclampsia and maternal/neonatal poor prognosis.

Results: The median ALBI score of the severe preeclampsia group was significantly higher than mild preeclampsia and control groups (p<0.001 and p<0.001 respectively). Also mild preeclampsia group had a higher ALBI score than the control group (p=0.039). The ROC curve analysis for the predictive value of ALBI score for maternal poor prognosis in preeclamptic patients showed an area under the curve (AUC) of 0.774 (95% CI 0.671 – 0.776, p<0.001). In the ROC curve analysis performed to investigate the value of ALBI score in neonatal poor prognosis prediction, the AUC was calculated as 0.55 (95% CI 0.48 – 0.62, p=0.164). For the prediction of preeclampsia with severe features in all preeclampsia cases, the AUC was 0.751 (95% CI 0.691-0.812, p<0.001)

Conclusion: The ALBI score could be a useful, cost-effective and practical liver function test and prognostic marker for patients with preeclampsia. However, the predictive performance for neonatal poor prognosis was not sufficient.

Keywords: Preeclampsia, albumin-bilirubin score, ALBI score

ÖZ

Amaç: Preeklampsili hastalarda albümin bilirubin (ALBI) skorunun bir karaciğer fonksiyon testi ve prognostik belirteç olarak kullanılabilirliğini değerlendirmek.

Gereç ve Yöntemler: Çalışmaya toplam 374 hasta dahil edildi (148 preeklampsi, 112 şiddetli bulguların eşlik ettiği preeklampsi, 114 kontrol). Üç grup arasında klinik ve demografik özellikler, laboratuvar bulguları ve ALBI skorları karşılaştırıldı. Ayrıca, preeklampsinin şiddeti ve maternal/neonatal kötü prognoz için ALBI skorunun prediktif değerinin tahmini için ROC eğrisi analizi yapıldı.

Bulgular: Şiddetli bulguların eşlik ettiği preeklampsi grubunun median ALBI skoru preeklampsi ve kontrol gruplarından anlamlı derecede yüksekti (sırasıyla p<0.001 ve p<0.001). Ayrıca, preeklampsi grubu kontrol grubundan daha yüksek ALBI skoruna sahipti (p=0.039). Preeklamptik hastalarda maternal kötü prognoz için ALBI skorunun prediktif değeri için yapılan ROC eğrisi analizinde eğri altında kalan alan (EAA) 0,774 (%95 CI 0,671 - 0,776, p<0,001) olarak bulundu. ALBI skorunun yenidoğan kötü prognoz tahminindeki değerini araştırmak için yapılan ROC eğrisi analizinde EAA 0,55 (%95 CI 0,48 - 0,62, p=0,164) olarak hesaplandı. Tüm preeklampsi olgularında şiddetli bulguların eşlik ettiği preeklampsi öngörüsü için EAA 0,751 (%95 GA 0,691-0,812, p<0,001) idi.

Sonuç: ALBI skoru preeklampsili hastalar için yararlı, uygun maliyetli ve pratik bir karaciğer fonksiyon testi ve prognostik belirteç olabilir. Ancak, neonatal kötü prognoz öngörüsündeki performansı yeterli değildir.

Anahtar Kelimeler: Preeklampsi, Albumin-bilirubin skoru, ALBI skoru

INTRODUCTION

Preeclampsia is described as a new onset of hypertension in the second half of the pregnancy or early postpartum period with the presence of proteinuria or end-organ damage (1). The prevalence of preeclampsia is 2-8% worldwide and it is one of the most important causes of morbidity and mortality in the pregnant population (2).

When decreased platelet (PLT) levels, impaired liver or kidney function, severe hypertension, neurological symptoms, or pulmonary edema are accompanied, the diagnosis becomes preeclampsia with severe features(1).

The ALBI score, which is based on the patient's albumin and total bilirubin levels, was first developed as a simple scoring system for

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Sorumlu Yazar/Corresponding Author: Osman Onur ÖZKAVAK, Ankara Bilkent City Hospital, Cankaya, Ankara, Türkiye
E-mail: onurozkavakdr@gmail.com

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the evaluation of disease severity in patients with hepatocellular carcinoma (HCC)(3). It defines worsening liver impairment across three grades (1 to 3). Also, its prognostic value for HCC patients treated by different methods (surgical resection, ablative treatment, transarterial or surgical therapies) has been shown by many studies (4). Afterward, its utility was evaluated in non-malignant liver diseases such as primary biliary cholangitis, chronic viral hepatitis B and C and autoimmune hepatitis and data has indicated that ALBI score/grade could serve a role as a prognostic marker in these conditions (5–11).

Furthermore, the prognostic value of ALBI score in non-liver diseases such as acute or chronic heart failure and acute pancreatitis was investigated and a higher ALBI score/grade was found to be associated with poor prognosis in these non-hepatic conditions (12–15).

Since impaired liver function is an important indicator of preeclampsia with severe features, we aimed to evaluate the ALBI score in patients with preeclampsia and its relation with disease severity, maternal and neonatal poor prognosis.

MATERIALS AND METHODS

The present study is a retrospective case-control study that includes data from pregnant women who followed up for preeclampsia and delivered in our hospital between May 2019 and December 2023, as well as healthy pregnant women who were followed up and delivered in our hospital on similar dates. The data of patients demographics and laboratory results were obtained from the delivery room, inpatient ward, operating room registry books and the hospital's electronic registration system. The study received approval from the local ethics committee with approval number E2-24-6195.

All consecutive preeclampsia cases who met the inclusion criteria were included and compared to a control group consisting of low-risk pregnant women at similar gestational ages. Multiple gestations, patients with additional chronic inflammatory conditions, malignancy, renal disease, liver disease, cardiac disease, or diabetes were excluded.

Preeclampsia cases were grouped based on the ACOG guidelines. Patients with a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg, recorded at least twice with a minimum interval at least 4 hours, accompanied by at least 2+ proteinuria measured by dipstick or 300 mg proteinuria within 24 hours, but without accompanying prodromal symptoms, pulmonary edema, seizures, impaired liver or kidney functions, and without thrombocytopenia, are classified as the preeclampsia group without severe features (1).

Patients with a systolic blood pressure of 160 mmHg or higher and/or a diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart, accompanied by severe persistent right upper quadrant or epigastric pain, severe analgesic-resistant headache, visual symptoms, pulmonary edema, impaired liver or kidney function, or thrombocytopenia are classified as preeclampsia with severe features (1).

Maternal poor prognosis is described as at least one of the following: Development of hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, eclampsia, admission to intensive care unit, or death. Neonatal poor prognosis is described as at least one of the following: first or fifth minute APGAR score < 5, admission to neonatal intensive care unit, birthweight < 2500 grams, delivery before 34 weeks, fetal or neonatal death.

The study only included data from patients who provided follow-up blood test results between weeks 30 and 34. Patients who did not provide blood test results during this time frame were excluded.

Gestational ages of the patients were determined using first-trimester crown-rump length measurements, typically taken between the 11th and 14th gestational weeks. The study compared demographic and clinical features such as maternal age, gravidity, parity, birth weights, gestational age at birth, APGAR scores, laboratory findings [hemoglobin level, white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count (PLT), urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST)], total bilirubin, albumin, ALBI scores between the three groups. ALBI scores were calculated using the formula (log10 bilirubinx0,66)+(albumin x -0,085) (3).

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 22, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). The Shapiro-Wilk test was employed to assess normality. As the data did not follow a normal distribution, non-parametric tests were utilized, and median values with interquartile ranges were reported for descriptive statistics. To compare data between groups, the Kruskal-Wallis and Mann Whitney U tests was performed. Receiver operating curve (ROC) analysis was employed to estimate the predictive value of the ALBI score for the severity of preeclampsia and maternal/neonatal poor prognosis. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 374 patients, with 148 patients categorized into the preeclampsia without severe features group, 112 patients in the preeclampsia with severe features group, and 114 cases enrolled in the control group. Among the preeclampsia group (comprising both cases with and without severe features), sixteen patients met at least one of the maternal poor prognosis criteria. Additionally, 132 neonates born to preeclamptic patients exhibited at least one of the neonatal poor prognostic factors.

Among the three groups, there was no statistically significant difference in gravidity, parity, hemoglobin level, lymphocyte count, monocyte count, platelet count and 5st minute APGAR scores.

The median age of the control group was significantly lower than both preeclampsia groups (p=0.023 and p=0.017 respectively). AST levels were significantly lower in the control group than in the preeclampsia and preeclampsia with severe features groups (p=0.002 and p<0.001 respectively), also the AST level of the preeclampsia with severe features group was significantly higher than the preeclampsia group (p<0.001). The ALT level of the control group was significantly lower than both preeclampsia groups (p=0.006 and p<0.001 respectively). The severe preeclampsia group had higher ALT levels than the preeclampsia group (p=0.037). The total bilirubin level was higher in the severe preeclampsia group than in the mild preeclampsia and control groups (p=0.016 and p=0.002 respectively). The albumin level of the control group was significantly higher than preeclampsia groups (p<0.001 and p<0.001 respectively), also the albumin level of the preeclampsia with severe features group was significantly lower than preeclampsia group (p<0.001).

The median ALBI score of the preeclampsia with severe features group was significantly higher than preeclampsia and control groups (p<0.001 and p<0.001 respectively). Also preeclampsia group had a higher ALBI score than the control group (p=0.039).

Gestational age at birth and birthweight of the preeclampsia with severe features group were significantly lower than preeclampsia and control groups (p=0.004, p=0.003; p<0.001, p<0.001 respectively). Also preeclampsia group had lower gestational age at birth and birthweight than control group (p<0.001 and p<0.001 respectively). 1st minute APGAR score of the control group was significantly higher than both preeclampsia groups (p<0.001 and p<0.001 respectively).

The comparison of demographic data, laboratory results, and neonatal outcomes between preeclampsia, preeclampsia with severe features and control groups are shown in Table 1.

The ROC curve analysis conducted to assess the predictive value of the ALBI score for maternal poor prognosis in preeclamptic patients yielded an area under the curve (AUC) of 0.774 (95% CI 0.671 – 0.776, p<0.001). Similarly, in the ROC curve analysis aimed at evaluating the predictive value of the ALBI score for neonatal poor prognosis, the AUC was determined to be 0.55 (95% CI 0.48 – 0.62, p=0.164). Subsequently, the optimal cutoff value for maximal sensitivity and specificity was calculated as -2.4, resulting in 81% sensitivity and 66% specificity for maternal poor prognosis, while achieving 50% sensitivity and 50% specificity for neonatal poor prognosis.

Furthermore, in predicting preeclampsia with severe features within all preeclampsia cases, the AUC was calculated as 0.751 (95% CI 0.691-0.812, p<0.001), with an observed sensitivity of 71% and specificity of 67% at a cutoff value of -2.5.

The results of ROC curve analyses are shown in Table 2, Figure 1-3.

DISCUSSION

Defective trophoblast invasion and placental ischemia are the mainstream of the pathophysiology of preeclampsia(16). As a result of placental ischemia, circulating levels of various factors and proinflammatory cytokines increase (16). These factors lead to maternal vascular remodeling, endothelial dysfunction and exaggerated inflammation; and these changes cause vascular narrowing, end-organ ischemia, platelet dysfunction and multiorgan damage, especially in the liver, kidneys and brain (2,17–19).

Periportal hemorrhage, ischemic changes and fibrinogen deposition were histologically demonstrated in liver examinations of patients with preeclampsia (20). A prospective study showed increased hepatic fibrosis in preeclamptic patients by using fibroscan performed in the postpartum first week (21). In a study that reports the histopathological findings of three autopsy cases of maternal deaths due to HELLP syndrome, periportal hepatocellular necrosis was the hallmark finding in the livers of the patients (22). As a result of hepatic injury, an increase in liver function tests such as AST and ALT is an important laboratory finding in patients with severe preeclampsia and its more life-threatening complication, HELLP syndrome.

In the current study, both the preeclampsia and preeclampsia with severe features groups exhibited elevated AST and ALT levels in comparison to the control group. In addition, within the preeclampsia cohorts, the severe features group demonstrated even higher AST levels than the mild group. Given that elevated

Table 1. Comparison of demographic data, laboratory results and neonatal outcomes between mild preeclampsia, severe preeclampsia and control groups

	Preeclampsia without severe features (n=148) (median, IQR)	Preeclampsia with severe features (n=112) (median, IQR)	Control group (n=114) (median, IQR)	p value
Age (years)	32 (11)	32 (13)	30 (7)	[a] 0.717 [b] **0.023** [c] **0.017**
Gravidity	2 (2)	2 (2)	2 (1)	0.442
Parity	0 (2)	1 (2)	1 (1)	0.146
Hemoglobin (g/dL)	11.9 (1.9)	12.2 (2.3)	11.8 (2.1)	0.056
WBC (x10^9/L)	10.49 (3.52)	11.35 (4.3)	9.87 (4.09)	[a] **0.003** [b] 0.374 [c] **0.008**
Neutrophil count (x10^9/L)	7,54 (3,42)	8.40 (4.4)	7.19 (3.55)	[a] 0.063 [b] 0.455 [c] 0.046
Lymphocyte count (x10^9/L)	1.99 (0.89)	1.92 (1.02)	1.75 (0.62)	0.076
Monocyte count (x10^9/L)	0.50 (0.24)	0.50 (0.24)	0.47 (0.20)	0.519
Platelet count (x10^9/L)	247 (102.25)	230 (111.5)	248 (104.3)	0.317
Urea (mg/dL)	20 (9)	24 (11)	17 (6)	[a] **0.003** [b] **<0.001** [c] **<0.001**
Creatinine (mg/dL)	0.55 (0.16)	0,62 (0.21)	0.49 (0.15)	[a] **0.007** [b] **0.006** [c] **<0.001**
AST (U/L)	21 (11)	29 (37)	17 (9)	[a] **<0.001** [b] **0.002** [c] **<0.001**
ALT (U/L)	14 (8)	16 (33)	12 (7)	[a] **0.037** [b] **0.006** [c] **<0.001**
Total bilirubin (mg/dL)	0.3 (0.2)	0.4 (0.3)	0.3 (0.2)	[a] **0.016** [b] 0.057 [c] **0.002**
Albumin (g/L)	37 (4)	33 (6)	38 (3)	[a] **<0.001** [b] **<0.001** [c] **<0.001**
Gestational age at birth (weeks)	37 (4)	34 (6)	39 (1)	[a] **0.004** [b] **<0.001** [c] **<0.001**
Birth weigth (grams)	2610 (975)	2065 (1546)	3220 (688)	[a] **0.003** [b] **<0.001** [c] **<0.001**
1st minute APGAR score	7 (1)	6 (1)	8 (1)	[a] 0.398 [b] **<0.001** [c] **<0.001**
5th minute APGAR score	9 (1)	8 (1)	9 (0)	0.515
ALBI score	-2.55 (0.32)	-2.20 (0.51)	-2.65 (0.25)	[a] **<0.001** [b] **0.039** [c] **<0.001**

[a]: Comparison between preeclampsia without severe features and preeclampsia with severe features
[b]: Comparison between preeclampsia without severe features and control groups
[c]: Comparison between preeclampsia with severe features and control groups
p<0.05 accepted as statistically significant. WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransfesase, BUN: blood urea nitrogen

liver enzymes serve as a diagnostic criterion for preeclampsia, our findings are consistent with the literature (1).

In preeclamptic patients, the timing of the delivery is an important issue. International guidelines recommend delivery at 37 $^{0/7}$ weeks in patients with preeclampsia without severe features and delivery between 34 $^{0/7}$ and 36 $^{6/7}$ weeks in patients with severe features. When maternal hemodynamic stability could not be achieved, earlier delivery should be considered (1,23). In our clinical practice, we plan our patients' deliveries in accordance with the guidelines.

Table 2. Reciever operating curve analysis results of predictive value of ALBI score for disease severity, maternal and neonatal poor prognosis*

Outcome	Cut-off	AUC	p	95%CI	Sensitivity	Specificity
Preeclampsia with severe features	-2.5	0.751	<0.001	0.691-0.812	71%	67%
Maternal poor prognosis	-2.4	0.774	<0.001	0.671-0.876	87%	62%
Neonatal poor prognosis	-2.4	0.550	0.164	0.480-0.620	50%	50%

p<0.05 accepted as statistically significant.
AUC: area under the curve, CI: confidence interval.
* Maternal poor prognosis described as at least one of the followings: Developement of HELLP syndrome, eclampsia or admission to intensive care unit. Neonatal poor prognosis described as at least one of the followings: first or fifth minute APGAR score < 5, admission to neonatal intensive care unit, birthweight < 2500 grams, delivery before 34 weeks, fetal or neonatal death.

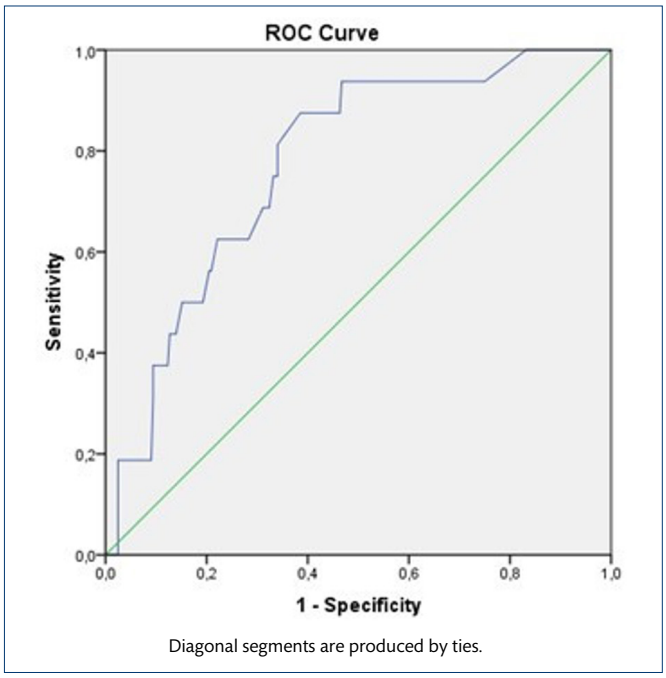

Figure 1. The ROC curve analysis for predictive performance of the ALBI score for maternal poor prognosis.

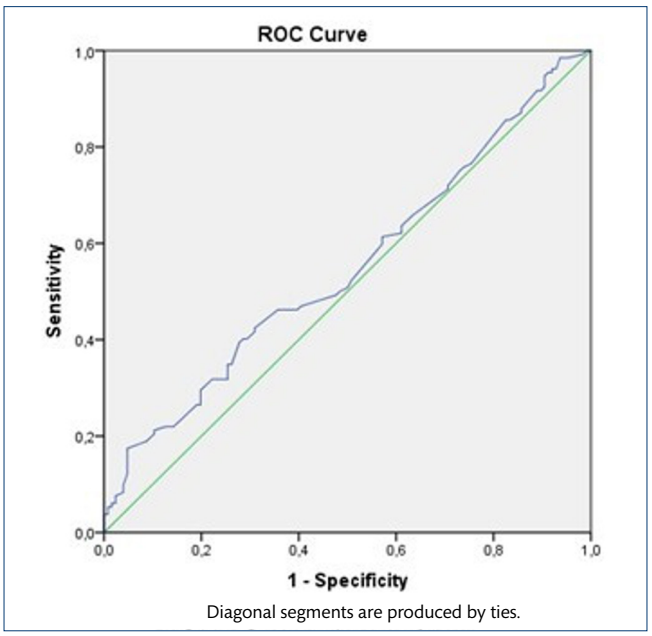

Figure 2. The ROC curve analysis for predictive performance of the ALBI score for neonatal poor prognosis.

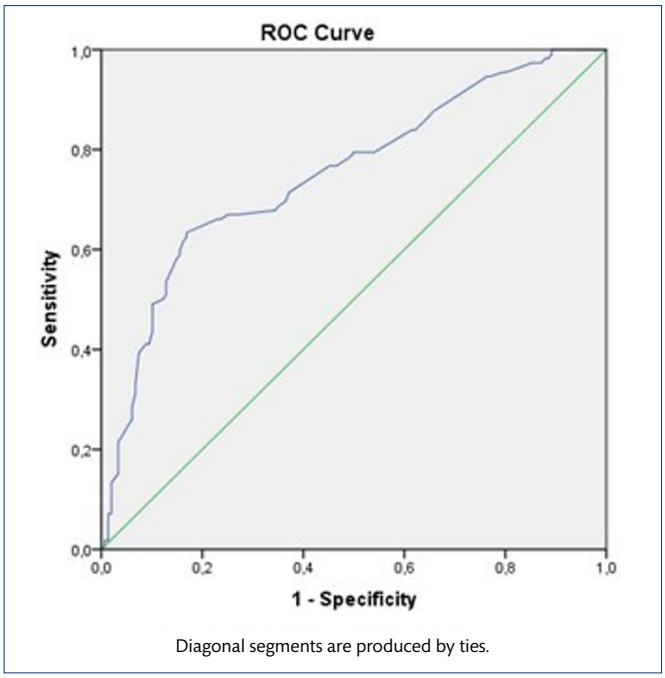

Figure 3. The ROC curve analysis for predictive performance of the ALBI score for severe preeclampsia.

Thus, our study showed lower gestational age at birth in both preeclampsia groups. As a result, we observed lower 1st minute APGAR scores in these groups.

Albumin synthesis is an important function of the liver. Thus, hypoalbuminemia reflects progressive hepatic damage in patients who diagnosed with liver disease (24). In our study, the group with the lowest albumin levels was the preeclampsia with severe features group, followed by the preeclampsia group and the highest albumin levels were observed in the control group and the difference between the three groups was statistically significant. These findings could indicate that hepatic damage may be present in all preeclamptic patients, and the severity of the disease may affect the synthesis function of the liver.

ALBI score was first described by Johnson et al. as a tool for assessment of disease severity in patients with HCC(3). Then they tested the model in several geographic regions and variable clinical

scenarios (patients undergoing resection, sorafenib treatment for advanced HCC and chronic liver disease but without HCC), and reported that the ALBI score provides a simple, objective, and discriminatory method of evaluating liver function in HCC. Its advantage to the classic Child-Pugh (CP) score is subjective findings such as encephalopathy and ascites are not required.

In a study involving 1242 patients, the predictive efficacy of the ALBI score for postoperative liver failure and long-term survival was assessed. The authors concluded that the ALBI score demonstrated superior performance compared to the CP grade in predicting these outcomes (25). Another retrospective study examined the association between the ALBI score and patient survival in live donor liver transplant recipients. The findings indicated that the ALBI score exhibited better performance than the Model for End-Stage Liver Disease (MELD) score for patient survival (26).

A prospective study that followed up 398 chronic hepatitis B-related liver cirrhosis over a median follow-up period of 33.9 months demonstrated that the ALBI score effectively forecasts both severity and long-term prognosis, surpassing the predictive accuracy the MELD score (6). Moreover, its prognostic reliability has been corroborated in patients with chronic hepatitis C infection and primary biliary chirrosis (8,9).

After these studies, the usefulness of the ALBI score in non-liver diseases became a field of investigation. In a multicenter, prospective study which enrolled 1190 patients with acute heart failure, higher ALBI scores was found to be associated with fluid overload and increased mortality (13). Similarly, another study reported a relationship between higher ALBI scores and inpatient mortality of patients with acute heart failure (14). In heart failure patients who required intensive care unit admission, short and long-term mortality rates were higher when the patients had higher ALBI scores (12). As well as, in a retrospective study that included the data of 284 patients who were admitted to the intensive care unit for severe acute pancreatitis, the ALBI score showed significant predictive performance for in hospital mortality and the authors reported that the performance of the ALBI score was superior to previously used scoring systems such as SOFA, SAPS-II, APACHE scores (15). Furthermore, higher ALBI scores were observed in patients with intrahepatic cholestasis of pregnancy in first trimester and at the time of the diagnosis, in a retrospective study (27).

In the present study, both the preeclampsia and preeclampsia with severe features groups had higher ALBI scores than the control group. Additionally, we observed a higher ALBI score in the preeclampsia with severe features group than in the preeclampsia group. As mentioned earlier, preeclampsia is associated with endothelial dysfunction and altered inflammation which results in end organ damage such as the liver, brain and kidneys. The increase in the ALBI score could be an indicator of the hepatic damage in patients with preeclampsia. Also the ROC curve analysis showed that the ALBI score has significant performance for prediction of the disease severity and maternal poor prognosis in patients with preeclampsia. Although, the predictive performance for neonatal poor prognosis was not sufficient.

This study's primary strength lies in its introduction of the ALBI score as a novel prognostic tool in preeclampsia, supported by a well-characterized patient cohort. However, the retrospective design may limit generalizability, and further prospective studies are needed to validate these findings. Despite this, the results provide a foundation for integrating liver function markers into clinical practice for improved maternal care.

CONCLUSION

The ALBI score represents a promising, cost-effective tool for evaluating liver function and predicting maternal outcomes in preeclampsia. Its simplicity and practicality make it a valuable addition to clinical practice, particularly in resource-constrained settings. However, the score's limited predictive value for neonatal outcomes highlights the need for further research to refine its applicability and explore potential combinations with other biomarkers. Future prospective and multicenter studies are essential to validate these findings and establish the ALBI score as a standard prognostic tool in preeclampsia management, thereby enhancing maternal and fetal healthcare outcomes globally.

Author Contributions

O.O.Ö.: Conception and design of the study; analysis and interpretation of the data and writing-review. D.S.: Conception and design of the study; analysis and interpretation of the data and writing-review.

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None

Conflict of Interest

The authors declare no conflict of interest.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Etiology and perinatal outcome of polyhydramnios: an experience of tertiary center

Polihidramnioz tanılı gebelerde etioloji ve perinatal sonuçlar

Ayşegül ATALAY[1], Tuğba Gül YILMAZ[2], Saliha SAĞNIÇ[3]

[1]Van State Education and Research Hospital, Department of Obstetrics and Gynecology, Division of Perinatology, Van, Türkiye
[2]Van State Education and Research Hospital, Department of Obstetrics and Gynecology, Van, Türkiye
[3]Van State Education and Research Hospital, Department of Obstetrics and Gynecology, Division of Gynecological Oncology, Van, Türkiye

ABSTRACT

Aim: To review our experience in fetuses with prenatally diagnosed with polyhydramniosis

Materials and Methods: Retrospective study of fetuses prenatally diagnosed with polyhydramniosis between October 2023 and January 2025 in a tertiary referral center.

Results: 104 pregnant women were included in the final analysis. When we classify the cases according to etiology of polyhydramnios, 31 (29.8 %) women had pregestational or gestational diabetes, in 8 (7.6 %) infants major structural or significant genetic anomalies were detected prenatally or postnatally, 65 (62.6 %) cases were classified as idiopathic and recent TORCH positivity was not observed in any of the cases 0 (0%). Most cases were delivered at term (81.8%), median gestational week at delivery was 36 (range, 23-41), and the mean standard deviation birthweight was 2996±969 grams. Polyhydramnios was more common in male than in female fetuses (67% vs 33%). Termination of pregnancy was selected in 1 (0.9%) of the cases diagnosed with acrania and performed at 23 weeks of pregnancy with fetocide. There were 2 intrauterine fetal demise at 32 and 35 weeks of gestation diagnosed with Trisomy 18 and cardiac anomaly respectively. 101 (97.1 %) were live born and 29 of 101 live born infants were needed neonatal intensive care unit.

Conclusion: Glucose tolerance test, detailed sonography, including fetal echocardiography should be performed in the pregnancies complicated with polyhydramnios. However, it is also reassuring for parents that the vast majority of cases are idiopathic.

Keywords: polyhydramnios, diabetes mellitus, outcome, etiology, idiopathic

ÖZ

Amaç: Prenatal dönemde polihidramniyoz tanısı konulan fetüslerdeki deneyimlerimizi gözden geçirmek

Gereç ve Yöntemler: Üçüncü basamak bir sevk merkezinde Ekim 2023 ile Ocak 2025 tarihleri arasında prenatal olarak polihidramniyoz tanısı alan fetüslerin retrospektif çalışması.

Bulgular: Çalışmaya dahil edilen 104 vakada, olguları polihidramnios etiyolojisine göre sınıflandırdığımızda, 31 (%29,8) pregestasyonel veya gestasyonel diyabet, 8 (%7,6) fetüste prenatal veya postnatal olarak majör yapısal veya genetik anomaliler tespit edildi, 65 (%62,6) olgu idiyopatik olarak sınıflandırıldı ve hiçbir olguda yakın zamanda TORCH pozitifliği gözlenmedi (%0). Olguların çoğu miadında doğum gerçekleşti (%81.8), doğumdaki medyan gebelik haftası 36 (23-41) ve ortalama doğum ağırlığı 2996±969 gramdı. Polihidramnios erkek fetüslerde kız fetüslere göre daha yaygındı (%67 vs. %33). Akrania tanısı konulan olguların 1'inde (%0,9) gebelik terminasyonu 23. gebelik haftasında fetosit ile gerçekleştirildi. Sırasıyla Trisomi 18 ve kardiyak anomali tanısı konulan 32 ve 35. gebelik haftalarında 2 intrauterin fetal ölüm tespit edildi. 101 fetüste (%97.1) canlı doğum ve canlı doğan 101 fetüsün 29'unda yenidoğan yoğun bakım ünitesinde takibe alındı.

Sonuç: Polihidramnios ile komplike olan gebeliklerde glukoz tolerans testi, fetal ekokardiyografi de dahil olmak üzere ayrıntılı sonografi yapılmalıdır. Bununla birlikte, vakaların büyük çoğunluğunun idiyopatik olması da ebeveynler için güven vericidir.

Anahtar Kelimeler: polihidramnios, diabetes mellitus, sonuç, etiyoloji, idiyopatik

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Sorumlu Yazar/Corresponding Author: Ayşegül ATALAY, Van State Education and Research Hospital, Department of Obstetrics and Gynecology, Division of Perinatology Süphan mah. Havalimanı kavşağı 1. km Edremit, 65000, Van, Türkiye
E-mail: draysegulatalay@gmail.com

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INTRODUCTION

Amniotic fluid (AF) is necessary for the normal growth and development of the human fetus. AF is obtained from the dialysis fluid, i.e. from the maternal serum that enters the amniotic cavity through the fetal membrane, the fetal lung exudate and the fetal skin, as well as from the fetal urine. While an adequate amount of AF can protect the fetus, abnormal amounts of AF can compromise the safety of the fetus and mother. Polyhydramnios is the excessive accumulation of AF and can occur in 1 – 2 % of pregnancies (1). The diagnosis is usually made sonographically by evaluating the SDP (Single Deepest Pocket) (2) or the AFI (Amniotic Fluid Index) (3) or by subjective sensation (4), and can be defined as SDP ≥ 8 cm, AFI ≥ 25 cm. Maternal and fetal conditions, including fetal structural and genetic anomalies, maternal gestational and pregestational diabetes, and TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster virus, parvovirus B19], rubella, cytomegalovirus, and herpes simplex virus infections) can lead to excess amniotic fluid, while 50–60% of polyhydramnios cases appear to be idiopathic (5-7). Polyhydramnios is associated with an increased risk of perinatal morbidity and mortality, including prematurity, aneuploidy, caesarean section, fetal structural anomalies, premature rupture of membranes (PROM), abnormal fetal presentation, umbilical cord prolapse and postpartum haemorrhage (8-10).

Pregnancy complicated by polyhydramnios can still pose a diagnostic and therapeutic dilemma for obstetricians, although the association between polyhydramnios and adverse perinatal outcomes has been reported repeatedly. The aim of our study was to review our experience of polyhydramnios cases and the respective perinatal outcome in a tertiary referral hospital.

MATERIALS AND METHODS

We performed a retrospective study on perinatal outcome of singleton pregnancies beyond 22 weeks of gestation diagnosed with polyhydramnios at the Department of Perinatology of Van Education and Research Hospital, between October 2023 and January 2025. This retrospective study was approved by the local ethics committee (no: GOKAEK/ 2025-01-04).

The sample size is based on all the pregnant women patients who were consulted to the perinatology outpatient clinic with a diagnosis of polyhydramnios from the antenatal outpatient clinic within the specified date range and whose diagnosis was confirmed by the perinatologist.

Ultrasound examinations were performed with a Voluson E8 system (GE Healthcare Medical Systems, Milwaukee, WI, USA) by the same resident. Polyhydramnios was defined as SDP ≥ 8 cm beyond 22 weeks of gestation (11) and detailed sonography was performed in all cases.

Diagnosis of polyhydramnios is routinely followed by performance of TORCH serology and review of oral glucose tolerance test (OGTT) results. In cases with associated prenatal or postnatal abnormalities or TORCH negative serologies or normal OGTT results with polyhydramniosis were advised to undergo fetal karyotyping. In the observed period OGTT was performed between 24 and 28 weeks of gestation by capillary blood analysis after 12 h of fasting and one and two hours after administration of 75 g glucose, and cut- off values for maternal diabetes mellitus were 92 / 180 / 153 mg/dl (12).

The inclusion criteria was singleton pregnancy, beyond 22 weeks of gestation. The exclusion criteria for the study were multiple pregnancies, pregnant women with missing TORCH serology. We searched our computerized database for prenatally diagnosed polyhydramnios and also performed a literature search to compare our data with those of previous series.

To perform this study, the following variables were also evaluated: Maternal age, gravidity, parity, previous miscarriage, living child, gestational week at diagnosis, presence of associated structural and genetic abnormalities, 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, and short-term outcomes.

Primary outcome parameter was the underlying etiology. For this analysis, the study group was retrospectively stratified into four groups: 1.) Recent TORCH infection (positive serology); 2.) Major structural anomalies or aneuploidies; 3.) Maternal gestational or pregestational diabetes; 4.) Idiopathic cases. In terms of severity, polyhydramnios was further categorized as mild or severe if the SDP was < 10 cm or ≥ 10 cm, respectively (1). Secondary outcome parameters were perinatal data including gestational age at birth, birth weight, mode of delivery, and neonatal mortality and morbidity. Fetuses with sonographic anomalies such as single umbilical artery, ventriculomegaly, macrosomia, mild renal pelvis dilatation in the prenatal period were not accepted as an anomalous group in the absence of additional structural and/or genetic anomalies in the postnatal period.

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. When the data were not

normally distributed, median values together with range were used. Mann-Whitney U test was performed for the comparison of median values amongst the groups. Categorical variables were presented as numbers and percentages.

RESULTS

During the specified period of the current study, 194 pregnancies were evaluated and of the 194 cases complicated with polyhydramnios, 90 cases were excluded from further analysis, and a total of 104 pregnant women were included in the final analysis Figure 1. When we classify the cases according to etiology of polyhydramnios, 31 (29.8 %) women had pregestational or gestational diabetes, in 8 (7.6 %) infants major structural or significant genetic anomalies were detected prenatally or postnatally, 65 (62.6 %) cases were classified as idiopathic and recent TORCH positivity was not observed in any of the cases 0 (0%) as presented in Figure 1.

The characteristics of the study population is presented in Table 1. Table 1 also outlines the associated major structural and/or genetic abnormal findings as detailed.

Table 2 summarize the fetal and neonatal outcomes of all cases with a prenatal diagnosis of polyhydramnios. Most cases were delivered at term (81.8%), median gestational week at delivery was 36 (range, 23-41), and the mean standard deviation (SD) birthweight was 2996±969 grams. In addition, polyhydramnios was more common in male than in female fetuses (67% vs 33%). Termination of pregnancy (TOP) was selected in 1 (0.9%) of the cases diagnosed

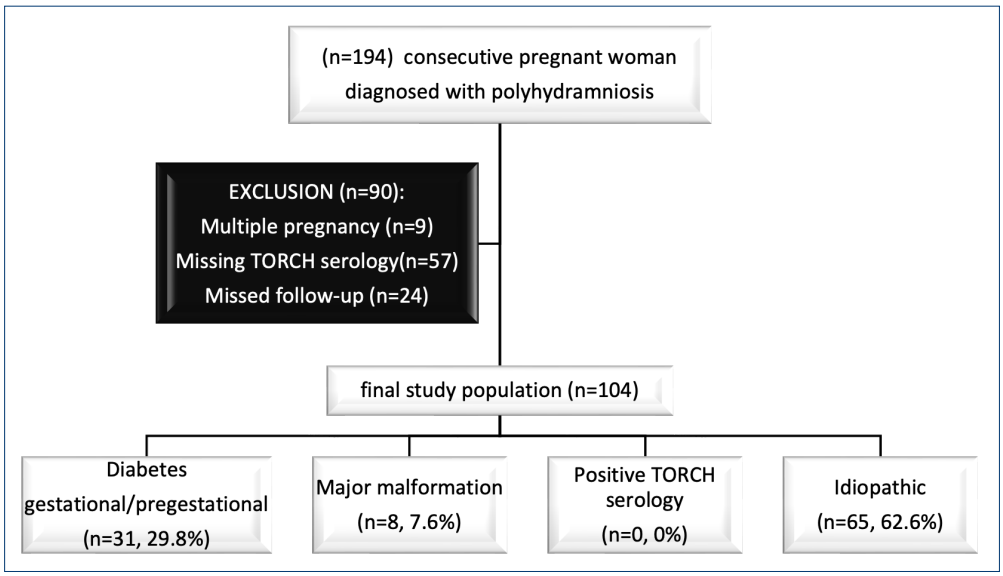

Figure 1. Flowchart illustrating study population selection and classification according to the etiology of polyhydramnios

Table 1. Characteristics and ultrasound findings of 104 pregnancies with a prenatal diagnosis of polyhydramnios

	Polyhydramnios(n=104)
Maternal age (median, min-max) (mean, SD)	30 (18-46) 30.1±6.54
Gravidity (median, min-max)	3 (1-12)
Parity (median, min-max)	2 (0-10)
Previous miscarriage (median, min-max)	0 (0-2)
Living Child (median, min-max)	1 (0-10)
Gestational week at diagnosis (median, min-max)	28 (24-41)
Major Fetal Anomalies (n, %) **Congenital heart defects** **Neural tube defects** **Cleft lip** **Holoprosencephaly** **Hipospadias** **Anal Atrezi** **Trizomi 18**	8 (7.6%)

Abbreviations: SD: standard deviation, min: minimum, max: maximum

Table 2. Fetal and neonatal outcomes of fetuses with a prenatal diagnosis of polyhydramnios

	(n=104)
GA at delivery (median, min-max)	36 (27-41)
Preterm delivery (<37 weeks) (median, min-max)	19 (18.2%)
Birth weight (grams) (mean, SD)	2996±969
Gender (n, %)	
Male	70 (67%)
Female	34 (33%)
Apgar at 1st minute (median, min-max)	8 (0-9)
Apgar at 5th minute (median, min-max)	9 (0-9)
Mode of delivery (n, %)	
Caesarean section	55(52.8%)
Vaginal delivery	49(47.2%)
Short term outcome (n, %)	
Termination of pregnancy	1 (0.9%)
Intrauterine fetal demise	2 (1.9%)
Live Birth	101 (97.1%)
Need for NICU	29 (27.8%)

Abbreviations: GA: gestational age, SD: standard deviation, min: minimum, max: maximum, NICU: need for neonatal intensive care unit

with acrania and performed at 23 weeks of pregnancy with fetocide. There were 2 intrauterine fetal demise (IUFD) at 32 and 35 weeks of gestation diagnosed with Trisomi 18 and cardiac anomaly (atrioventricular septal defect), respectively. Among the 104 cases of polyhydramnios, 101 (97.1 %) were live born. 29 of 101 live born infants were needed neonatal intensive care unit (NICU).

While mild polyhydramnios was observed in the majority of the diabetic and idiopathic polyhydramnios group 61% and 68% respectively, it was observed in only 25% of the patients in the anomalous group.

DISCUSSION

In the present study, we conducted a retrospective study on the etiology and perinatal outcome of polyhydramnios to improve information for counseling and management of affected pregnant women in our hospital. It is noteworthy that the vast majority of polyhydramnios cases (62.6%) were idiopathic with no evidence of fetal or maternal pathology, which should be communicated at informed consent. However, in the remaining 29.8% we found maternal diabetes, fetal structural or genetic abnormalities (7.6%) as causes of the condition. Although most cases of polyhydramnios are idiopathic, when an etiology is identified, it is most commonly due to a fetal anomaly or maternal diabetes. Our study findings are consistent with earlier reports on polyhydramnios and the respective etiology (13-15).

In our study, while maternal diabetes was found to be the most common etiology for polyhydramnios, which is consistent with the literature, none of the polyhyramnios cases was found to be associated with TORCH infection (16).

The most common associated anomalies in our study were cardiac and neural tube defects (NTD). Although NTDs often show sonographic findings during routine antenatal sonography, the prenatal detection rate of congenital heart anomalies is only 16.7 % (14, 16). We therefore strongly recommend that fetal echocardiography be included in the diagnostic work-up of cases with polyhydramnios.

Demographic data analysis in the current study showed that polyhydramnios was more common in younger women; the median maternal age in our study was 30 years, whereas in the literature it is conflicting. Biggio et al. found an association between idiopathic polyhydramnios and increasing maternal age and parity (13), while Khan et al. found it more common in younger women (17). Same study reported low Apgar scores at one minute and five minutes (17). In our study, we found no association between polyhydramnios and low Apgar scores.

In the literature, the incidence of aneuploidy in infants with polyhydramnios is between 0.4 and 3.2 % (8, 13, 18). Brady et al. reported an incidence of 3.2% and therefore advocated performing amniocentesis (18), while others did not recommend routine karyotyping in sonographically isolated polyhydramnios.

Unfortunately, in our study, the prevalence of genetic abnormalities was only 0.9%, because pregnant women did not accept genetic diagnostic invasive techniques. This condition is one of the limitations of current study. Our study have also other limitations, since it was retrospectively designed and reports a single-center experience.

CONCLUSION

To summarize, a glucose tolerance test, a detailed sonography, including fetal echocardiography, should be performed in the pregnancies complicated with polyhydramnios. However, it is also reassuring for parents that the vast majority of cases are idiopathic. It is important to note that idiopathic polyhydramnios is a diagnosis of exclusion. While the cause may be unclear during pregnancy, the cause may become apparent after birth.

Ethical approval
Ethics approval was obtained from the institutional review board. The study was conducted in accordance with the Declaration of Helsinki.

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Authors contributions
All authors contributed to the study conception and design and meet the ICMJE criteria for authorship. Material preparation, data collection and analysis were performed by [Aysegul Atalay] and [Tugba Gul Yılmaz]. The first draft of the manuscript was written by [Aysegul Atalay].[Saliha Sagnic] commented on previous versions of the manuscript and study supervision. All authors read and approved the final manuscript.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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İlk trimester serum inflamatuar markerlarını kullanarak gebelik kolestazını öngörebilir miyiz?

Can we predict cholestasis of pregnancy using first trimester serum inflammatory markers?

Birsen KONUKÇU[1], Tuğba KARABULUT[2]

[1]Antalya Şehir Hastanesi Perinatoloji Ünitesi, Antalya, Türkiye
[2]Elazığ Fethi Sekin Şehir Hastanesi Kadın Hastalıkları ve Doğum Kliniği, Elazığ, Türkiye

ÖZ

Amaç: Gebelik kolestazı maternal ve fetal etkilerinden dolayı ciddi bir hastalıktır. Bu nedenle son zamanlarda gebelik kolestazının erken tanısı ve hastalık gelişebilecek kişilerin öngörülmesi üzerine çeşitli çalışmalar yapılmaktadır. Biz de bu amaçla ilk trimester hemogram inflamatuar markerları ve karaciğer fonksiyonlarını gösteren markerlardan, gebelik kolestazını öngörebilmek adına bir çalışma tasarladık.

Gereç ve Yöntemler: Ocak 2022-Ocak 2024 yılları arasında kliniğimize başvuran gebelik kolestazı olguları (n:31) ve benzer sayı (n:31) ve demografik özelliklerdeki kontrol grubu çalışmaya dahil edilmiştir. Retrospektif olarak laboratuvar verileri ve doğum sayıları incelenmiş ve analiz edilmiştir.

Bulgular: Vaka ve kontrol grubunun ilk trimesterda verdiği kan sonuçları incelendiğinde Ortalama trombosit hacmi (mean platelete volüme MPV), eritrosit dağılım genişliği (Red cell distribution width RDW) %, aspartat aminotranferaz (AST), alanin aminotransferaz (ALT), Aspartat aminotransferaz (AST)- trombosit oranı indeksi (APRI), Aspartat aminotransferaz- alanin aminotransferaz oranı indeksi (AARI) değerleri arasında istatistiki anlamlı sonuçlar elde edilmiştir. MPV, AST, ALT VE APRI değerleri kolestaz grubunda daha yüksek bulunurken, RDW% ve AARI değerleri kontrol grubunda daha yüksek bulunmuştur.

Sonuç: Artmış MPV, AST, ALT VE APRI değerleri ve azalmış RDW% ve AARI değerleri, kolestaz ile ilişkilidir ve gebelik kolestazı için tanı algoritmasına kullanılmak için uygun parametreler olabilir. Sorumlu altta yatan moleküler patojenik mekanizmaları değerlendirmek için daha büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gebelik kolestazı, riskli gebelikler, antenatal tarama

ABSTRACT

Aim: Intrahepatic cholestasis of pregnancy (ICP) is a serious condition due to its maternal and fetal effects. Therefore, various studies have recently been conducted on the early diagnosis of ICP and the prediction of individuals at risk. With this aim, we designed a study to predict ICP using first-trimester hemogram inflammatory markers and markers indicating liver functions.

Materials and Methods: Cases of ICP (n=31) and a control group of similar number (n=31) and demographic characteristics who presented to our clinic in the between of January 2022-January 2024 were included in the study. Laboratory data and delivery numbers were retrospectively reviewed and analyzed.

Results: When the first-trimester blood results of the case and control groups were examined, statistically significant results were obtained between mean platelet volume (MPV), red cell distribution width percentage (RDW%), aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST to platelet ratio index (APRI), and AST to ALT ratio index (AARI) values. MPV, AST, ALT, and APRI values were found to be higher in the cholestasis group, while RDW% and AARI values were higher in the control group.

Conclusion: Increased MPV, AST, ALT, and APRI values and decreased RDW% and AARI values are associated with cholestasis and may be suitable parameters to use in the diagnostic algorithm for ICP. Larger studies are needed to evaluate the underlying molecular pathogenic mechanisms responsible.

Keywords: Pregnancy cholestasis, high-risk pregnancies, antenatal screening

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Sorumlu Yazar/Corresponding Author: Birsen KONUKÇU, Antalya Şehir Hastanesi Perinatoloji Ünitesi, Antalya, Türkiye
E-mail: birsenkonukcu@hotmail.com

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GİRİŞ

Gebeliğin intrahepatik kolestazı (GİK) gebeliğin ikinci üçüncü trimesterlerinde ortaya çıkan gebeliğe özgü en yaygın karaciğer hastalığıdır. Sıklıkla kaşıntı ve karaciğer transaminazlarının yüksekliği ile bulgu verir. Gebelikte karaciğer fonksiyon testlerinde artışa neden olan preeklampsi akut yağlı karaciğer gibi durumlardan veya kaşıntıya sebep olan diğer gebelik dermatozlarından, açlık safra asiti yüksekliği (≥10 µmol/L) ile ayrılır (1). GİK'nin rapor edilen insidansı, ülkeler ve popülasyonlar arasında %0,2 ile %22 arasında değişmektedir (2,3) İntrahepatik kolestazın nedeni belirsizliğini korumaktadır, ancak genetik faktörler, beslenme yardımcı üreme teknikleri, oral kontraseptif (OKS) kullanımı gibi predispozan faktörleri olan, kanaliküler zar boyunca anormal biliyer transport ile karakterize, etiyolojisi kompleks ve heterojen bir hastalıktır (2,4) Bu hastalık, anne için ciddi mortalite ve morbidite riski oluşturmaz, belirtileri genellikle doğumdan sonra 48 saat içinde çözülür ve laboratuvar anormallikleri 2-8 hafta içinde normalize olur (5,6) ve doğum sonrası sekelsiz iyileşir. Fetüs için preterm doğum, mekonyumla boyalı amniyotik sıvı, travay sırasında fetal distress ve antepartum ölüm gibi ciddi riskler taşımaktadır (7). Serum safra asitleri 40 µmol/L yüksek olan olgularda, fetal ölüm riskinin anlamlı oranda arttığı bilinmektedir (8). Tedavide temel amaç hastanın semptomplarını gidermek ve fetal etkilerin önüne geçmektir(9,10). Kullanılan tek tadavi ursodeoksikolik asit uygulamasıdır.

Klinik bulgular başladıktan sonra açlık safra asiti değerinin elde edilmesi ve tedaviye başlanması zaman almaktadır. Ayrıca intrauterin gelişme geriliği, preeklampsi gibi cidi fetal adverse etkileri bulunan hastalıkları erken haftalarda öngörmek için çeşitli testler üzerinde çalışılsa da GİK için yapılan çalışmalar çok kısıtlıdır.

Son zamanlarda, Aspartat aminotransferaz (AST)- trombosit oranı indeksi (APRI), pediatrik hastalarda kolestatik karaciğer hastalıklarını ve fibrozisi tanılamak için kullanılmıştır. Bu çalışmalara göre, APRI skoru paranteral beslenme ile ilişkili kolesatasisin gelişiminde güvenilir ve invaziv olmayan bir belirteç olabilir ve kolesatik karaciğer hastalığı olan hastalarda hafif ve ileri fibrozisi ayırt etmek veya karaciğer transplantasyonu sonrası greft fibrozunu değerlendirmede kullanılabilir (9,10). Ayrıca, Aspartat aminotransferaz- alanin aminotransferaz oranı indeksi (AARI), primer biliyer sirozu olan hastalarda siroz belirteci olarak araştırılmış ve sirozun tanısında klinik değere sahip olduğu bildirilmiştir. Obstetrik uygulamada, günlük kullanımda ICP gelişimini erken tahmin etmek için APRI ve AARI oranı araştırılmış ve çalışmalarda erken tanı ve GİK şiddetini belirlemek için tanı değeri olan testler olarak değerlendirilmiştir (3,11–13).

Ayrıca son literatürde, rutin tam kan hücresi (CBC) sayısının bazı bileşenlerinin, malignitelerin, kardiyovasküler hastalıkların, otoimmün hastalıkların ve bazı gebelik patolojilerinin tanısında yardımcı olabileceği gösterilmiştir (14,15) . CBC değerleri ve GİK arasındaki ilişki mevcut literatürde yetersiz olarak çalışılmıştır. Gebelikle CBC bileşenleri arasındaki ilişkiyi inceleyen yalnızca üç çalışma bulduk (16–18). 2017 yılında yapılan bir Türk çalışmasında, Yayla Abide ve arkadaşları, MPV'nin üçüncü trimesterde şiddetli GİK vakalarında hafif GİK veya kontrol grubuna göre daha yüksek olduğunu tespit etmişlerdir (16). Ayrıca Türkiye'de, 2014 yılında, Kirbas ve arkadaşları, hafif GİK ve şiddetli GİK grubunda normal gebeliklere göre daha yüksek Nötrofil / lenfosit oranı (NLR) düzeyleri buldular (17).

Biz bu çalışmalar ışığında, ilk trimester hemogram ve biyokimya değerleri ile GİK öngörüsü için literatüre katkıda bulunmak ve önceki araştırmaları genişletmek istedik ve Türkiye'deki bir popülasyonda gebeliğin ilk trimesterında CBC bileşenleri ve ICP arasındaki ilişkiyi, APRI ve AARI oranının GİK öngörüsündeki yerini tespit etmek amacıyla çalışmamızı başlattık.

GEREÇ VE YÖNTEM

Elazığ şehir hastanesi, Elazığ, Türkiye'de Ocak 2022-Ocak 2024 yılları arasında GİK tanısı konulan ve gebelik takipleri ve doğumları hastanemizde gerçekleştirilen 31 GİK olgunun klinik verileri retrospektif olarak tarandı. Veriler retrospektif olarak toplandığından, bilgilendirilmiş onam gerekli değildi. Bu çalışma, Helsinki Bildirgesi'nde belirtilen prensiplere göre yerel etik kurulu tarafından onaylanmıştır (E-71522473-050.01.04-5774-02) İkinci veya üçüncü trimesterde, dermapatolojik bir tanısı olmayan yaygın kaşıntıya sahip hastalara, yüksek serum AST, ALT veya açlık safra asidi, normal hepatobiliyer ultrasonografik görüntüleme bulguları ve hepatit A, B ve C için negatif serolojik test sonuçları ile GİK tanısı konuldu. Çoğul gebelikleri, kronik sistemik veya otoimmün veya endokrinolojik hastalıkları, karaciğer hastalıkları, hematolojik veya enfeksiyöz hastalıkları ve son bir yılda kan ürünü transfüzyonu olan hastalar çalışmadan çıkarıldı. Kontrol grubu, gebelik öncesi veya gebeliğe özgü herhangi bir hastalığı olmayan, gebelik takipleri hastanemizde yapılan ve çalışma grubundaki hastalarla aynı dönemde hastanemizde doğum yapan rastgele seçilmiş sağlıklı 31 gebe kadından oluştu.

Çalışmadaki ilk amacımız gebelik kolestazı tanısı konulan olguların gebelik ve yenidoğan sonuçlarını incelemek ikincil amacımız ise GIK ve sağlıklı gebeler arasında birinci trimesterlerde WBC, hemoglobin, nötrofil, lenfosit, NLR, PLR, RDW, trombosit, MPV AST, ALT, APRI VE AARI seviyelerini karşılaştırmaktı.

Olgu grubunun tanı aldığı hafta, tanı anındaki transaminaz değerleri, tanı anıdaki açlık safta asiti değerleri, gebelik takibinde veya doğum esnasında obstetrik problemler gelişmişse bu durumlar veri olarak kaydedildi.

Kontrol grubu olarak seçilen hastalar ve vaka grubu için de yaş, gravida, parite, abort, vücut kitle indeksi (VKİ), birinci trimester CBC eğerleri, B12, ferritin ve AST, ALT düzeyleri kaydedildi. Hastaların doğum raporlarına ulaşılıp doğum yaptıkları haftalar, doğum şekilleri, bebeğin doğum kilosu boyu ve cinsiyeti kayıt altına alındı.

İlk trimester APRI skoru, literatürde belirtildiği gibi hesaplandı [(AST/normal üst sınır)/trombosit sayısı (10^9 L–1) × 100]. (3,12) AST normal üst sınır 40 IU/L olarak alındı. İlk trimester AARI oranları şu formül kullanılarak hesaplandı: serum AST (IU/L) /ALT (IU/L). (3,19) Hastanemizin laboratuvarında kullanılan sisteme göre AST için normal üst sınır 40 U/L, ALT için 40 U/L ve açlık safra asidi için 10 µmol/L idi.

Bu çalışmada tüm istatistiksel analizler için IBM Corp., Armonk, NY, ABD tarafından geliştirilen Statistical Package for the Social Sciences (SPSS) 25.0 kullanıldı. Çalışmanın verilerin değerlendirilmesinde tanımlayıcı istatistiksel yöntemler kullanıldı. Üzerinde durulan özelliklerden sürekli değişkenler için tanımlayıcı istatistikler; Ortalama ± Standart Sapma olarak ifade edilirken, kategorik değişkenler için sayı ve yüzde olarak ifade edildi. Verilerin dağılımı Kolmogorov Smirnov testi ile test edildi. Normal dağılıma sahip veriler için parametrik bağımsız iki örnekli t-testi ve normal dağılım göstermeyen veriler için parametrik olmayan Mann Whitney U-testi kullanıldı. Tüm değerler için $p < 0.05$ düzeyinde anlamlılık düzeyi değerlendirildi. İlk trimester APRI skoru ve AARI skoru değerlerinin GİK gelişimini öngörmek için kesim noktalarını belirlemek için ROC analizi yapıldı. Tüm istatistiksel analizlerde, iki yönlü p değeri <0.05 istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Hastane verilerimiz incelendiğinde çalışmamız kapsamında dahil edilme ve dışlanma kriterlerini karşılayan 31olguya ulaşıldı. Aynı sayıda benzer yaş ve demografik özelliklerde ve yine hastanemizde doğum yapan 31 kadın da kontrol grubu olarak çalışmamıza dahil edildi. Gebelik kolestazı tanısı ile takip edilmiş hastaların ortalama anne yaşı 30,5±6,1 yıl, Ortalama tanı haftası 30.16±4,01hafta, tanı anında hastaların ortalama ALT değeri 136,24±121,9 U/L, AST değeri 83,34±59,5 U/L ve ortalama serum safra asitleri değeri 29,7±20.1 µmol/L idi. Ortalama total bilirubin seviyesi 0,73±0.51 mg/dL, ortalama GGT düzeyi 19,85±9,16 U/L, ortalama LDH düzeyi 260,07±67,21 U/L, ortalama ALP düzeyi 204,23±66,67 U/L olarak bulunmuştur. Kontrol grubu ile karşılaştırıldığında demografik veriler, bebek doğum kilosu doğum haftası açısından iki grup arasında fark tespit edilmemiştir. Veriler Tablo 1'de gösterilmiştir.

14 hastada ursodeoksikolik asit tedavisi gebelik boyunca 250 mg. 3x1 pozolojide uygulanırken 7 hastada kliniğin gerilememesi nedeniyle ursodeoksikolik asit tedavisi maksimum doza (250 mg 3x2) çıkılmıştır.

Kolestaz hastalarında ortalama doğum haftası 37±2,73 ve doğum ağırlığı 2834±576 gramdı. 8 doğum (%25,8) normal vajinal yolla olurken, 23 doğum (%74,2) sezeryan yoluyla gerçekleşmiştir. 8 olguda fetal distres gelişmiş, 6 olguda amnion mayide mekonyum izlenmiş, 9 olguya preeklampsi eşlik etmiş ve 10 olguda intrauerin gelişme geriliği (IUGR) gözlenmiştir.

Kontrol grubunda ise doğumların %58,1'i (n:18) normal vajinal yolla gerçekleşirken, %41,9 u (n:13) sezeryan yoluyla gerçekleşmiştir.

Vaka ve kontrol grubunun ilk trimesterda verdiği kan sonuçları incelendiğinde MPV, RDW % AST, ALT, APRI, AARI değerleri arasında istatistiki anlamlı sonuçlar elde edilmiştir. İlk trimester hemogram parametreleri ve biyokimya değerleri arasındaki karşılaştırma Tablo 2'de gösterilmiştir.

Tablo 1. Kolestaz ve kontrol grubunun demografik ve doğum verileri açısından karşılaştırılması

	Kontrol (Ort±SS)	Kolestaz (Ort±SS)
Yaş	29,39 ± 5,34	30,52 ± 6,14
Gravida	2,26 ± 1,37	2,23 ± 1,26
Parite	0,97 ± 1,11	0,9 ± 1,01
Doğum haftası	38,58 ± 1,36	37 ± 2,73
Bebek KG	3350,26 ± 353,78	2834,52 ± 576,71
Bebek boyu	49,03 ± 3,64	48,19 ± 2,37

KG: Kilogram Ort: Ortalama SS: Standart Sapma

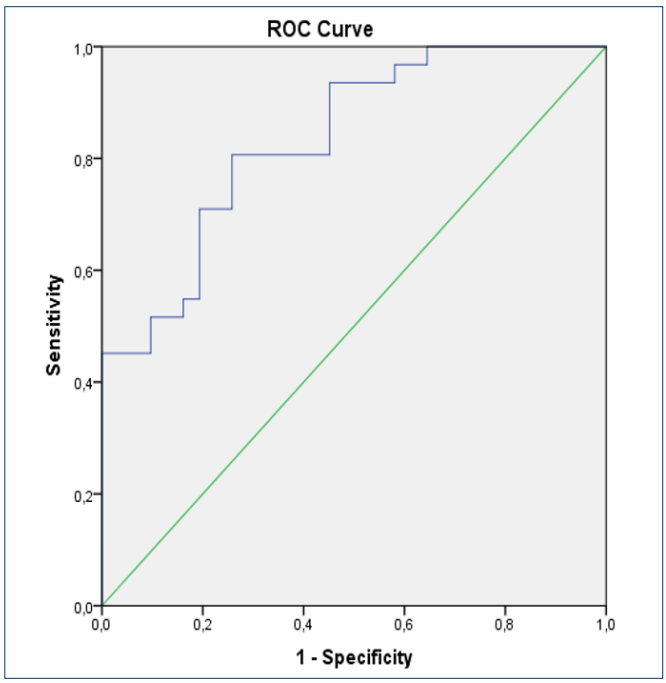
Tablo 2. Kolestaz olgu ve kontrol grubu ilk trimester hemogram ve biyokimya değerleri.

Değişken Ortalama (SS)	KONTROL		KOLESTAZ		Test İst.	P değeri
	Ortalama (SS)	Ortanca (min-maks)	Ortalama (SS)	Ortanca (min-maks)		
HB (g/dL)	12,6 (1,22)	12,7 (8,2 - 14,11)	12,45 (1,14)	12,5 (9,8 - 14,6)	414,5	0,352
HCT* %	37,58 (3,01)	37,5 (29,1 - 42,8)	36,9 (3,17)	36,3 (30,4 - 43,6)	0,871	0,387
WBC (10^9 /L)	8,67 (1,95)	8,17 (5,96 - 12,74)	8,39 (1,4)	8,7 (5,8 - 11,4)	457	0,740
PLT (10^9 L^{-1})	265,97 (45,34)	252 (210 - 349)	263 (56,12)	250 (170 - 348)	477	0,960
NEU (10^9 /L)	5,9 (1,58)	5,99 (3,72 - 9,84)	5,78 (1,17)	6,09 (3,4 - 7,86)	467	0,849
LYM (10^9 /L)	2,12 (0,6)	2,01 (1,33 - 3,52)	4,42 (8,33)	1,89 (0,3 - 32,9)	431	0,485
NLR	2,93 (0,92)	2,44 (1,29 - 4,51)	3,58 (3,18)	3,12 (0,16 - 18)	414	0,349
PLR	134,12 (40,23)	134,04 (70,59 - 213,33)	154,98 (115,03)	135,88 (7,14 - 663,33)	439	0,558
MPV (f/L)	8,51 (1,09)	8,4 (6,6- 10,8)	10,33 (1,09)	10 (7 - 13)	115,5	<0,001*
RDW %	13,93 (1,29)	13,5 (11,5 - 18,8)	14,88 (1,46)	14,8 (12,7 - 19,9)	266	0,002*
RDW (fL)	42,58 (2,59)	42,4 (38,1 - 50,2)	44,14 (4,04)	42,4 (39,4 - 61)	362	0,095
AST (IU/L)	14,48 (3,17)	14 (8 - 20)	27,97 (15,66)	22 (14 - 80)	96,5	<0,001*
ALT(IU/L)	12,58 (4,94)	11 (5 - 29)	31,94 (25,38)	24 (8 - 124)	129,5	<0,001*
APRI	0,14 (0,04)	0,14 (0,06 - 0,23)	0,28 (0,18)	0,2 (0,12 - 0,83)	159	<0,001*
AARI	1,25 (0,4)	1,2 (0,64 - 2,8)	1,03 (0,37)	0,91 (0,57 - 2)	302,5	0,012*

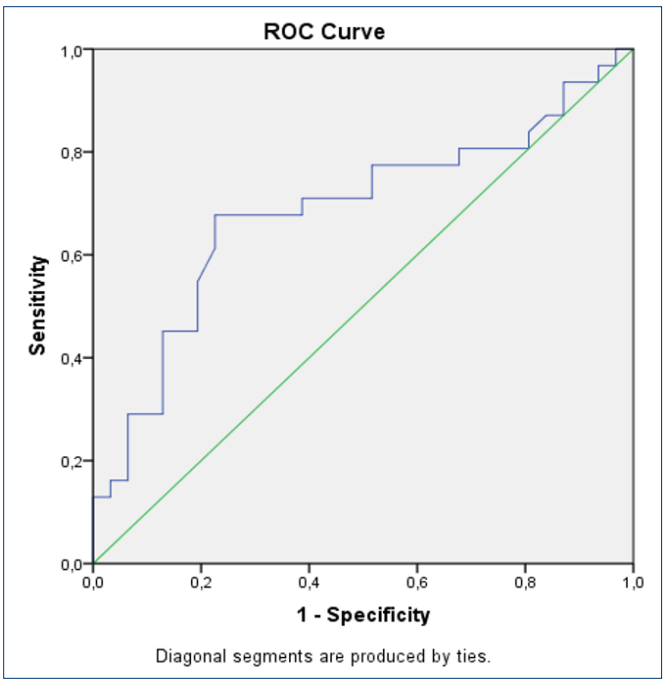
HCT Değeri homojen dağılım gösterdiği için Independent samples t test uygulanmıştır. Diğer değerlerin analizinde Mann Whitney U test kullanılmıştır.
SS: standart sapma Min: minimum Maks: Maksimum HB: Hemoglobin HCT: Hematokrit WBC: Beyaz küre sayısı PLT: Platelet MPV: Ortalama platelet volume, NEU: Nötrofil LYM: Lenfosit RDW: Red blood cell distribution width, , RDW: Red blood cell distribution width, NLR: Neutrophil-to-lymphocyte oranı, PLR: Platelet-to-lymphocyte oranı

GİK gelişiminin özellikle ilk trimester APRI, AARI skoru ile AST, ALT, MPV ve RDW % değerleri ile öngörülebileceği belirlenmiştir (Tablo 2).

Özellikle ilk trimester APRI skoru, üçüncü trimester GİK gelişimini belirlemede istatistiksel olarak anlamlıdır (p<0.001), ve ROC eğrisi değeri 0.835'dir. APRI skoru için kesim noktası değeri >0,16 olarak kabul edildiğinde, duyarlılığı %71 ve özgüllüğü %74'tür (Tablo 3).



Şekil 1. APRI ROC eğrisi analizi



Şekil 2. AARI ROC eğrisi analizi

ROC: Receiver operating characteristic; APRI: Aspartate aminotransferase/platelet oran index
Aspartate aminotransferase / Alanine aminotransferase; oran inex AUC: Curve altında kalan alan

Tablo 3. Gebelikte intrahepatik kolestazın (GIK) öngörülmesi için APRI skoru ile AARI skorunun ROC eğrisi

Test	AUC	Cutoff	Duyarlılık%	Özgüllük%	G.Aralığı	P değeri
APRI	0,835	0,16	71	74	0,738-0,932	0,00
AARI	0,685	1,06	67	61	0,548-0,822	0,012

ROC: Receiver operating characteristic; APRI: Aspartate aminotransferase/platelet oran index
Aspartate aminotransferase / Alanine aminotransferase; oran inex AUC: Curve altında kalan alan

TARTIŞMA

Gebelik kolestazı maternal ve fetal mortalite ve morbiditeyi artırmasından ötürü, çok sayıda çalışma ilk trimesterda GİK'i öngörebilmek için tasarlanmıştır. İlk trimesterdaki anoploidi taraması için bakılan PAPP-A değerindeki azalma, maternal lipit profilindeki artış gibi parametreler GİK ile ilişkili bulunmuştur. (20,21) Hastaların hepsine antenatal tarama testi yapılmadığı ve maternal lipit profili rutin ilk trimester tetkiklerinden olmadığı için, her hastaya uygulanan tarama testleri arasından yeni markerlar elde edilmeye çalışılmıştır. Literatürde bununla ilgili göze çarpan çalışmalar vardır (3,11–13,22,23).

APRI, kronik hepatit C'li hastalarda karaciğer fibroz ve sirozun non-invaziv bir indeksi olarak tanımlanmıştır (24) ve daha sonra pediatrik karaciğer nakli hastalarında uzun dönem graft fibrozunun değerlendirilmesinde kullanılmıştır (25). Kronik karaciğer hastalığı olan gebelerde yapılan farklı bir çalışmada, APRI'nin sirozlu hastalarda sirozlu olmayanlara göre anlamlı olarak daha yüksek olduğu bulunmuş ve APRI'nin kronik karaciğer hastalığı olan hastalarda doğumun tahmininde kullanılabileceği belirtilmiştir(26).

Daha önceki çalışmalarda gebeliğin ilk trimesterında bakılan yüksek APRI ve düşük AST/ALT oranının, üçüncü trimesterda GİK gelişimi ile ilişkili olduğu görülmüştür (3,11–13). Ayrıca Eyisoy ve arkadaşları yüksek APRI seviyelerini mekonyumlu amnion, yenidoğan yoğun bakıma giriş oranları ve preterm doğum ile ilişkili bulmuştur. Tolunay ve arkadaşları APRI ile GİK arasındaki ilişkiyi incelemişlerdir. Bu çalışmada APRI'nin formülasyonu net olarak belirtilmese de (11), GİK'li hastaların ilk trimester APRI değerinin kontrol grubuna göre anlamlı derecede daha yüksek olduğu ($p<0.001$) ve GİK'i öngörmek için APRI'nin cutoff noktası değerinin 0.57 olarak tespit edildiği belirtilmiştir. Saadi ve arkaaşları APRI cutoff değerini 0,42 olarak verirken (22), GOK ve arkadaşları 0,17 (12), Kale ve arkadaşları APRI cutoff değerini 0,14 olarak vermiştir(3). APRI için optimal kesim noktalarındaki farklılığın, APRI'nin farklı formüllerle hesaplanmasından kaynaklandığını düşünmekteyiz. Biz bu çalışmada, ilk trimester APRI değerini önceki referans çalışmalara dayanarak Kale, Gok ve arkadaşlarının kullandığı gibi aşağıdaki formül kullanılarak hesapladık.

Serum AST (IU/L)/normal üst sınır x 100/trombosit sayısı (10^9/L), AST normal üst sınırımız 40 IU/L olarak alındı.

Yakın zamanda yayınlanan Sakcak ve arkadaşlarının yaptığı çalışmada ise GİK olan hastalarda kontrol grubu ile karşılaştırıldığında anlamlı olarak daha yüksek APRI skorları vardı ROC analizinde, APRI skorunun ikinci-üçüncü trimesterde GİK'i öngörme kesme değeri, %78 duyarlılık ve %79 özgüllük ile 0,092 idi. APRI skoru ile yenidoğan yoğun bakım ünitesi (YYBÜ) gereksinimi arasında anlamlı pozitif bir ilişki olduğunu gösterdi (27).

AST/ALT oranının, alkol kötüye kullanımı olan hastalarda(28), kronik hepatit C'li hastalarda (29) ve primer sklerozan kolanjitli hastalarda (19) ikincil karaciğer sirozu gelişimini tespit etmek için kullanılabilen invaziv olmayan, güvenilir bir belirteç olduğu gösterilmiştir. Bu hastalarda yüksek AST/ALT oranının, kötü sonuçlar ve karaciğer sirozu için güvenilir bir gösterge olduğu bulunmuştur. Bu bilgiler ışığında, erken gebelikte GİK' nın tahmininde APRI' ye ek olarak ilk trimester AST/ALT oranını araştıran çalışmalar mevcuttur (3). Bu çalışmaya göre, GİK' li hastaların ilk trimester AST/ALT oranı, sağlıklı kontrol grubundan anlamlı derecede daha düşüktür. Bizim çalışmamızda da bu veriyi destekler şekilde AST/ALT (AARI) oranını kontrol grubuna göre daha düşük bulduk. ROC eğrisinden elde edilen sonuçlara göre %67 duyarlılık %61 özgüllükle cuttof değeri 1,06 olarak tespit edilmiştir. Çalışmamızda, referans aralık içinde olsa da yüksek ilk trimester AST ve ALT değerlerinin, GİK öngörmede değerli olduğu sonucuna vardık. Kontrol grubu ortalama AST değeri 14,48 ±3,27 bulunurken kolestaz grubu AST değeri 27,97±15,66 olarak bulunmuştur. ALT değerlerinde ise yine sırasıyla kontrol grubunda 12,58±4,94 kolestaz grubunda 31,94 ± 25,38 olarak bulunmuş, bu değerler arasında istatistiki anlamlı sonuçlar elde edilmiştir.

Bu çalışmamızda ayrıca her hasta için bakılan değerler arasından, ancak inflamatuar belirteçler olarak dikkat çeken NLR, PLR, MPV ve RDW' nin GİK ile ilişkisini araştırmayı amaçladık. Elde ettiğimiz sonuçlara göre MPV ilk trimester değeri kolestaz olgularında kontrol grubuna göre anlamlı derecede yüksek bulundu. Bu bulgular daha önce yapılan Abide ve arkadaşları ve Silva ve arkadaşlarını destekler nitelikteydi (16,18). MPV altta yatan bir inflamatuar süreçle ilişkili klinik koşullarda yükselir ve bu nedenle birçok tıbbi durumda seyir ve prognozu gösteren bir belirteç olarak kullanılabilir. Bir trombosit

aktivitesi belirteci olan MPV, trombosit sayısına yanıt olarak değişir. İnflamatuar patolojik koşullarda, inflamatuar aracıların üretimi nedeniyle artmış bir trombosit agregasyonu ve daha büyük trombositlerin yüzdesinde artış görülür, bu da MPV'de artışa neden olur (30).

Çalışmamızda, birinci trimesterde kontrol grubuna oranla ve GİK olgularında RDW› nin daha düşük olduğunu gözlemledik. Bu, Yayla Abide ve arkadaşlarının 2017'de yayımlanan çalışmasını destekler niteliktedir (16), Silva ve arkadaşlarının yaptığı çalışmada iste RDW düzeyinde gruplar arası anlamlı fark bulunmamıştır(18). Yine aynı çalışmada GİK grubunda kontrol grubuna kıyasla NLR' da belirgin bir azalma gözlemlenirken, Kirbas ve arkadaşlarının yaptığı bir çalışmada NLR'da belirgin bir artış bulunmuş (17), Yayla Abide ve arkadaşlarının çalışmasında NLR seviyeleri her iki grup arasında benzer bulunmuştur (16). Bizim verilerimiz de Abide ve arkadaşlarını destekler nitelikte olup iki grup arasında anlamlı fark elde edilememiştir. Çelişen sonuçlar, çalışmamızdaki sınırlı vaka sayısıyla açıklanabilir.

Gebelikle ilişkili komplikasyonların önlenmesi, komplikasyonların yönetimi ve tedavisi kadar önem arz etmektedir. GİK gelişiminin erken tahmini, neonatal ve perinatal komplikasyonların gelişimini önleyebilir. Bu bağlamda, ilk trimester hemogram parametrelerinden MPV ve RDW deki değişikler ve APRI ve AST/ALT oranının hesaplanıp değerlendirilmesi erken GİK tanı ve öngörüsü konusuna yardımcı olabileceği düşünülse de çalışmanın retrospektif doğası, tek merkezli olması ve sınırlı sayıda hastanın olması çalışmanın kısıtlamalarıdır.

SONUÇ

Sonuç olarak, ilk trimester APRI skoru ve AST/ALT oranı, erken GİK tahmininde kullanılabilecek kolay, ucuz ve invaziv olmayan bir araçtır. Altta yatan moleküler patojenik mekanizmaları değerlendirmek ve bu çalışmada bulunan eğilimleri daha fazla araştırmak için daha büyük çalışmalara ihtiyaç vardır. Gelecekteki çalışmalar tarafından doğrulandığında, CBC ve biyokimya bileşenlerinden bazıları ve oranları, GİK için yeni bir tanısal algoritmayı oluşturmak için dahil edilebilir.

Bu çalışmanın sonuçlarının büyük hasta sayıları ve çok merkezli prospektif çalışmalarla desteklenmesi gerektiğine inanıyoruz.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Evaluating ChatGPT's effectiveness in providing medical information for pregnant women with rheumatic diseases

Romatizmal hastalığı olan hamile kadınlara tıbbi bilgi sağlamada ChatGPT'nin etkinliğinin değerlendirilmesi

Bahar ÖZDEMİR ULUSOY[1], Can Ozan ULUSOY[2]

[1]Ankara Gaziler Physical Therapy and Rehabilitation Training and Research Hospital, Department of Rheumatology, Ankara, Türkiye
[2]Ankara Etlik City Hospital, Department of Perinatology, Ankara, Türkiye

ABSTRACT

Aim: The growing use of ChatGPT as a source of health information highlights the need to assess its accuracy and adequacy. This study evaluated the accuracy and adequacy of ChatGPT (version 3.5) in responding to frequently asked questions from pregnant women with rheumatic diseases in both Turkish and English, aiming to assess its potential as a reliable source of patient information across languages in rheumatology and maternal-fetal medicine.

Materials and Methods: A total of 36 questions related to pregnancy and rheumatic diseases were obtained from Google and divided into seven subgroups. Questions were posed to ChatGPT in both Turkish and English and responses were evaluated on a 4-point scale by a rheumatologist (Expert 1) and a perinatologist (Expert 2). Mann-Whitney U test was used for statistical analysis ($p < 0.05$ was considered significant).

Results: ChatGPT's English responses demonstrated a higher rate of accuracy and completeness compared to its Turkish responses. In English, 91.6% of answers were rated as correct, compared to 75.0% in Turkish. Expert 1 rated the average score for Turkish responses as 3.64 ± 0.54 and for English responses as 3.89 ± 0.31, a difference that was statistically significant ($p = 0.023$). Expert 2 rated Turkish responses with an average score of 3.83 ± 0.37 and English responses with an average score of 3.94 ± 0.23, with no statistically significant difference ($p = 0.136$).

Conclusion: ChatGPT demonstrates promise as an accessible source of information for pregnant women with rheumatic disease, but has limitations in its non-English responses. This highlights the need for improvement in language-specific training of language models. Further research is recommended to explore the performance of ChatGPT across multiple languages and medical specialties.

Keywords: ChatGPT, rheumatic diseases, pregnancy, language models, patient education

ÖZ

Amaç: ChatGPT'nin bir sağlık bilgi kaynağı olarak artan kullanımı, doğruluğunun ve yeterliliğinin değerlendirilmesi ihtiyacını vurgulamaktadır. Bu çalışmada, ChatGPT'nin (versiyon 3.5) romatizmal hastalığı olan hamile kadınların sıkça sorduğu sorulara Türkçe ve İngilizce yanıt vermedeki doğruluğu ve yeterliliği değerlendirilerek, romatoloji ve anne-fetal tıbbı alanlarında farklı dillerde güvenilir bir hasta bilgi kaynağı olma potansiyeli değerlendirilmiştir.

Gereç ve Yöntemler: Gebelik ve romatizmal hastalıklarla ilgili toplam 36 soru Google'dan elde edildi ve yedi alt gruba ayrıldı. Sorular, ChatGPT'ye hem Türkçe hem de İngilizce olarak yöneltildi ve yanıtlar, bir romatolog (Uzman 1) ve bir perinatolog (Uzman 2) tarafından 4 puanlık bir ölçekle değerlendirildi. İstatistiksel analiz için Mann-Whitney U testi kullanıldı ($p < 0.05$ anlamlı kabul edildi).

Sonuçlar: ChatGPT'nin İngilizce yanıtları, Türkçe yanıtlarına kıyasla daha yüksek bir doğruluk ve tamlık oranı göstermiştir. İngilizcede yanıtların %91,6'sı tam doğru olarak değerlendirilirken, Türkçede bu oran %75,0 olmuştur. Uzman 1, Türkçe yanıtlar için ortalama puanı 3,64 ± 0,54 ve İngilizce yanıtlar için 3,89 ± 0,31 olarak değerlendirmiştir; bu fark istatistiksel olarak anlamlıdır ($p = 0,023$). Uzman 2, Türkçe yanıtları ortalama 3,83 ± 0,37 ve İngilizce yanıtları ortalama 3,94 ± 0,23 puanla değerlendirmiştir ve istatistiksel olarak anlamlı bir fark yoktur ($p = 0,136$).

Tartışma: ChatGPT, romatizmal hastalığı olan hamile kadınlar için erişilebilir bir bilgi kaynağı olarak umut vaat etmekte, ancak İngilizce olmayan yanıtlarında sınırlamalar bulunmaktadır. Bu durum, dil modellerinin dile özgü eğitiminde iyileştirme gereğini vurgulamaktadır. ChatGPT'nin birden fazla dil ve tıbbi uzmanlık alanındaki performansını keşfetmek için daha fazla araştırma yapılması önerilmektedir.

Anahtar Kelimeler: ChatGPT, romatizmal hastalıklar, gebelik, dil modelleri, hasta eğitimi

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Sorumlu Yazar/Corresponding Author: Bahar ÖZDEMIR ULUSOY, Ankara Gaziler Physical Therapy and Rehabilitation Training and Research Hospital, Department of Rheumatology, 06100 Ankara, Türkiye
E-mail: bharozdemir@gmail.com

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INTRODUCTION

In recent years, artificial intelligence (AI)-based large language models (LLMs) have revolutionized access to information and have begun providing guidance across various fields. One such model, ChatGPT, developed by OpenAI, is a conversational AI agent with powerful text-processing capabilities. Named the Generative Pretrained Transformer (GPT) 3.5, this model is designed to understand and respond to text-based questions, generate text, and perform various language-related tasks (1). ChatGPT can answer users' questions as if they were engaged in a conversation with a human. By synthesizing information from the internet, it presents complex topics in a summarized and understandable way, making it frequently used in many areas, including medical consultation (2).

One of ChatGPT's standout features is its ability to detect the language in which a question is asked and respond in the same language. This capability makes it an accessible and effective source of information for a global audience. Its clear and fluent writing style, combined with the ability to communicate in nearly any language, makes ChatGPT a versatile tool. In the medical field, ChatGPT is increasingly used for patient education and preliminary health guidance, offering accessible explanations for complex medical topics (3). For example, pregnant women with rheumatic diseases can turn to ChatGPT to learn about the effects of their condition on pregnancy and possible treatment options, receiving answers in their native language. However, the accuracy and medical adequacy of these responses require careful scrutiny to assess their reliability.

Pregnant women with rheumatic diseases frequently seek information on how their condition may affect pregnancy, medication safety, and potential risks during childbirth. To meet this need, many patients and their families turn to search engines or AI-based conversational agents. Especially during the sensitive period of pregnancy, receiving accurate responses to these inquiries is of great importance.

In this study, we identified the most frequently asked questions on Google by pregnant women with rheumatic diseases and posed these questions to the free version of ChatGPT in both Turkish and English. We then evaluated the responses on a 4-point scale based on our medical knowledge, current medical guidelines, and clinical experience as a rheumatologist and a perinatologist (4-9). Our evaluation focused on the scientific validity of ChatGPT's information, as well as the accuracy and depth with which it answered patients' questions. Our study aims to understand to what extent artificial intelligence can serve as a reliable source of information for patients and healthcare professionals in these specific medical fields.

MATERIAL AND METHODS

In this study, a total of 36 frequently asked questions regarding pregnancy and rheumatic diseases were obtained from Google services (10) and categorized into seven subcategories: "Basic Knowledge," "Ankylosing Spondylitis," "Rheumatoid Arthritis," "Psoriatic Arthritis," "Systemic Lupus Erythematosus,"

Table 1. List of questions asked by 2 experts to ChatGPT version 3.5

Question No	Question
1	Do rheumatic diseases affect my baby's development?
2	Is there a risk of premature birth due to rheumatic diseases?
3	Can rheumatic diseases cause congenital problems in my baby?
4	Can people with rheumatic diseases have children?
5	Is rheumatism medication used during pregnancy?
6	Does inflammation in the body harm the child?
7	Is high CRP an obstacle to getting pregnant?
8	How do rheumatic diseases affect my pregnancy?
9	Do rheumatic diseases worsen or improve during pregnancy?
10	Do rheumatic diseases require cesarean delivery?
11	Can a person with rheumatism have a normal delivery?
12	What should I do if my rheumatic disease flares up during pregnancy?
13	What can I do for rheumatic pains during pregnancy?
14	Is ankylosing spondylitis an obstacle to pregnancy?
15	Does ankylosing spondylitis cause problems during delivery?
16	Can ankylosing spondylitis be passed on to the baby?
17	Is rheumatoid arthritis exacerbated during pregnancy?
18	How does rheumatoid arthritis affect pregnancy?
19	Can rheumatoid arthritis be passed on to the baby?
20	Are the medicines used to treat rheumatoid arthritis safe during pregnancy?
21	Is psoriatic rheumatism an obstacle to pregnancy?
22	Does psoriatic rheumatism make it difficult to get pregnant?
23	Does psoriatic rheumatism worsen during pregnancy?
24	Can psoriatic rheumatism be passed on to the baby?
25	Does psoriatic rheumatism affect labor?
26	Are the medicines used to treat psoriatic rheumatism safe during pregnancy?
27	How does systemic lupus erythematosus (SLE) affect pregnancy?
28	Does lupus flare during pregnancy?
29	Can SLE be passed on to the baby?
30	Does scleroderma affect my ability to get pregnant?
31	What are the risks of scleroderma during pregnancy?
32	Can a mother with scleroderma pass the disease on to her baby?
33	Which medicines can a patient with scleroderma use during pregnancy?
34	Is colchicine used in pregnancy?
35	Does cortisone during pregnancy harm the baby?
36	Is biological therapy safe during pregnancy?

"Scleroderma," and "Medication." These questions, listed in Table 1, were directed to ChatGPT version 3.5 (OpenAI) in both Turkish and English (11). To maintain consistency and minimize variability, each question was asked once in both languages at the same time interval. This approach prevented potential variations in responses that might arise if the same question were asked multiple times or at different times, as ChatGPT can generate differing answers under such conditions. Responses were scored by two experts with at least 5 years of experience in their field: Expert 1, a rheumatologist, and Expert 2, a perinatologist. Answers were assessed on a 4-point scale based on completeness and alignment with established guidelines. A "4-point correct answer" was awarded for responses that were 100% complete and accurate according to medical guidelines. Answers with over 50% correct information were classified as "3-point partially correct answers," while those with less than 50% accuracy received "2-point inadequate answer" scores. Responses containing any misinformation were rated as "1-point incorrect answers (Figure 1)."

Each expert independently reviewed and rated the responses in both languages, ensuring a consistent and objective evaluation process. The experts' assessments reflected the completeness and reliability of the information provided by ChatGPT.

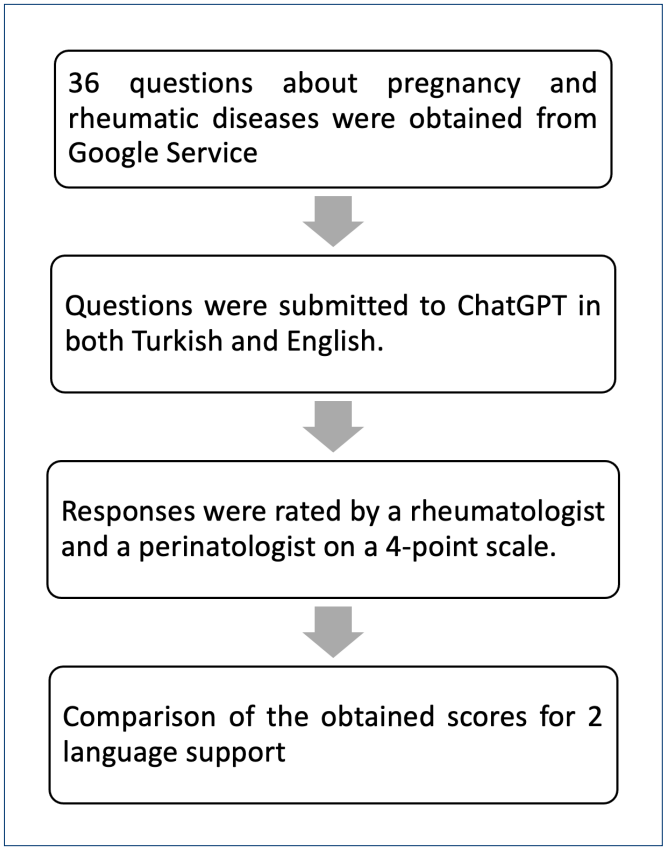

Figure 1. Flowchart of the planning of the study

Statistical analyses

All statistical analyses were carried out using SPSS version 29 (SPSS Inc., Chicago, IL, USA) Statistical analyses included a normality test (Shapiro), and since the data did not follow a normal distribution, the Mann-Whitney U test was used. Statistical significance was defined as $p < 0.05$. This methodology ensured a rigorous evaluation of ChatGPT's capacity to provide accurate and medically reliable information for pregnant individuals with rheumatic conditions.

RESULTS

Table 2 shows the categorization of ChatGPT's answers to the Turkish and English questions asked by Expert 1 and Expert 2 in terms of their accuracy. In the Basic Knowledge category, 100% of the English responses were rated correct by Expert 1, while Expert 2 found 92% of responses correct and 8% partially correct. Turkish responses, however, showed more variability; Expert 1 rated 54% as correct and 46% as partially correct, whereas Expert 2 found 92% correct and 8% partially correct.

In the Ankylosing Spondylitis category, all responses in both languages were rated as 100% correct by both experts. For the Rheumatoid Arthritis category, Expert 1 rated 75% of the English responses as correct and 25% as partially correct, while Expert 2 found all responses correct. In Turkish, both experts agreed, with 75% of responses rated as correct and 25% as partially correct.

For the Psoriatic Arthritis category, Expert 1 rated 83% of English responses as correct and 17% as partially correct, while Expert 2 found all responses correct. Turkish responses were rated 50% correct and 50% partially correct by Expert 1, while Expert 2 rated all responses as correct.

In the SLE category, both experts rated 100% of the English responses as correct. For Turkish responses, Expert 1 found 100% correct, whereas Expert 2 rated 75% correct and 25% partially correct. In the Scleroderma category, 75% of the English responses were rated correct by Expert 1, with 25% as partially correct, while Expert 2 found all responses correct. Turkish responses showed more variability; Expert 1 rated 75% as correct and 25% as partially correct, while Expert 2 rated 50% correct and 50% partially correct.

In the Medication category, both experts rated 67% of English responses as correct and 33% as partially correct. Turkish responses, however, displayed a more complex pattern: Expert 1 rated 67% as correct and 33% as mixed and misleading, while Expert 2 rated 67% correct and 33% partially correct.

Table 2. Evaluation of ChatGPT's responses to rheumatic disease questions during pregnancy in turkish and english by expert review

N (%)	English		Turkish	
N:36	**Expert 1**	**Expert 2**	**Expert 1**	**Expert 2**
Basic Knowledge (n:13)				
Partially correct	0 (0)	1 (8)	6 (46)	1 (8)
Correct	13 (100)	12 (92)	7 (54)	12 (92)
Ankylosing Spondylitis (n:3)				
Partially correct	0 (0)	0 (0)	0 (0)	0 (0)
Correct	3 (100)	3 (100)	3 (100)	3 (100)
Rheumatoid Arthritis (n:4)				
Partially correct	1 (25)	0 (0)	1 (25)	1 (25)
Correct	3 (75)	4 (100.0)	3 (75)	3 (75)
Psoriatic Arthritis (n:6)				
Partially correct	1 (17)	0 (0)	3 (50)	0 (0)
Correct	5 (83)	6 (100)	3 (50)	6 (100)
Systemic Lupus Erythematosus (n:3)				
Partially correct	0 (0)	0 (0)	0 (0)	1 (25)
Correct	3 (100)	3 (100)	3 (100)	3 (75)
Scleroderma (n:4)				
Partially correct	1 (25)	0 (0)	1 (25)	2 (50)
Correct	3 (75)	4 (100)	3 (75)	2 (50)
Medication (n:3)				
Mixed and misleading	0 (0)	0 (0)	1 (33)	0 (0)
Partially correct	1 (33)	1 (33)	0 (0)	1 (33)
Correct	2 (67)	2 (67)	2 (67)	2 (67)
TOTAL				
Mixed and misleading	0 (0.0%)	0 (0.0%)	1 (3.5%)	0 (0.0%)
Partially correct	4 (11.1%)	2 (5.6%)	11 (30.5%)	6 (16.6%)
Correct	32 (88.8%)	34 (94.4%)	24 (66.6%)	30 (83.3%)

Expert 1: Rheumatologist; Expert 2: Perinatologist

Table 3. Comparison of mean scores for turkish and english responses by expert evaluation with standard deviation and statistical significance.

	Expert 1	Expert 2	P value
Turkish answers, mean ± SD	3.64 ± 0.54	3.83 ± 0.37	0.096
English answers, mean ± SD	3.89 ± 0.31	3.94 ± 0.23	0.397
P value	0.023	0.136	

In the total results, neither expert rated any responses as mixed and misleading in English (0%), whereas in Turkish, Expert 1 rated 3.5% as mixed and misleading. For partially correct responses, Expert 1 rated 11.1% in English and 30.5% in Turkish, while Expert 2 rated 5.6% in English and 16.6% in Turkish. Finally, correct responses were rated at 88.8% by Expert 1 and 94.4% by Expert 2 in English, compared to 66.6% by Expert 1 and 83.3% by Expert 2 in Turkish. ChatGPT answered 91.6% of the total 72 English questions asked by both experts correctly, while 8.4% were partially correct. In total 72 Turkish questions, 75.0% of them were correct, 23.6% were partial correct and 1.3% were mixed and misleading.

Table 3 shows the statistical analysis of the scores given by Expert 1 and Expert 2. Expert 1's average score for Turkish responses was 3.64 ± 0.54, compared to 3.89 ± 0.31 for English responses, and this difference was statistically significant ($p = 0.023$). Expert 2 rated Turkish responses with an average score of 3.83 ± 0.37 and English responses with an average score of 3.94 ± 0.23, with no statistically significant difference ($p = 0.136$). Additionally, there were notable differences between Expert 1 and Expert 2's scores within each language. For Turkish responses, Expert 2's average score (3.83 ± 0.37) was slightly higher than Expert 1's (3.64 ± 0.54), although this difference was not statistically significant (p =

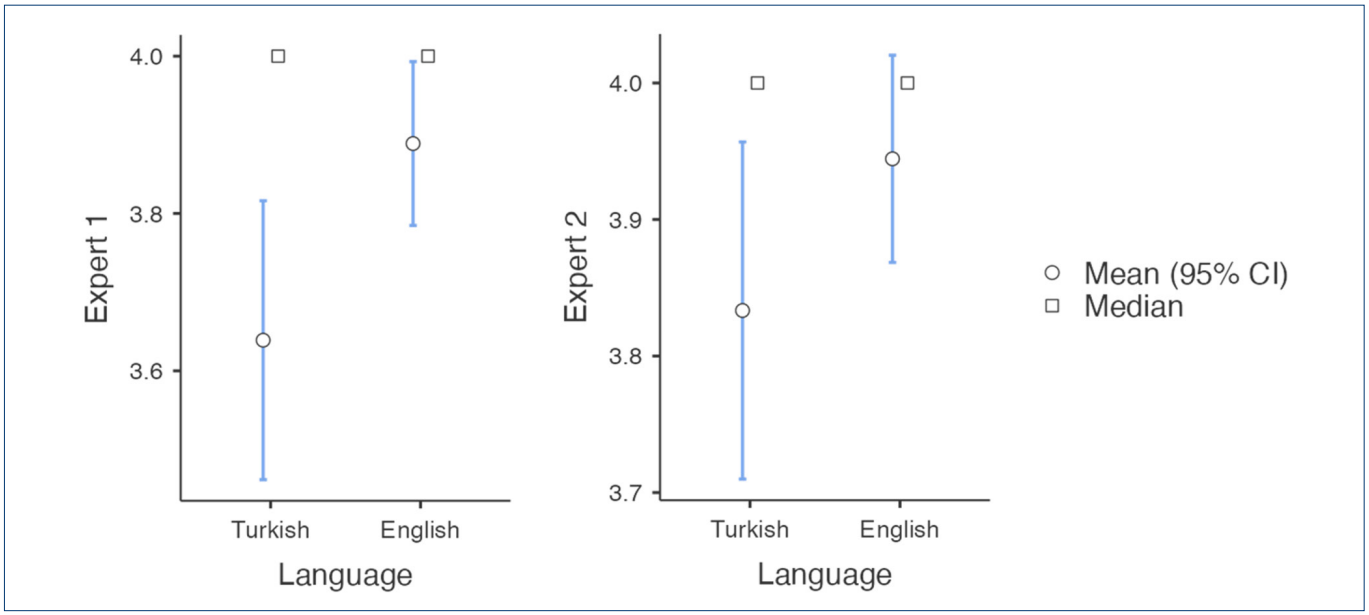

Figure 2. Mean and median scores with 95% confidence ıntervals for Turkish and English responses by expert evaluation

0.096). In the case of English responses, Expert 2 again awarded slightly higher average scores (3.94 ± 0.23) compared to Expert 1 (3.89 ± 0.31), but this difference also did not reach statistical significance (p = 0.397).

Figure 2 illustrates the mean and median scores, along with the 95% confidence intervals, for ChatGPT's responses in both Turkish and English, as evaluated by Expert 1 and Expert 2. As shown, English responses consistently received slightly higher mean scores from both experts compared to Turkish responses. This aligns with the data presented in Table 3, where a statistically significant difference was observed between languages in Expert 1's evaluation (p = 0.023), while Expert 2's evaluations did not show a significant difference (p = 0.136).

DISCUSSION

The findings of this study reveal that ChatGPT generally provides accurate or partially accurate responses to frequently asked questions regarding rheumatic diseases in pregnancy, both in English and Turkish. Although English responses demonstrate a higher rate of full accuracy, Turkish responses are also found to be satisfactory. However, notable differences in completeness and accuracy between the two languages suggest that ChatGPT's potential for providing information may vary depending on language support and the model's ability to grasp subtle linguistic nuances. These findings indicate that, while ChatGPT could be a valuable tool for patient education in healthcare, improvements in language support could enhance its effectiveness.

The use of LLMs like ChatGPT in the medical field is rapidly expanding, with ChatGPT frequently employed to respond to queries across diverse domains. Its application in medical contexts, including diagnosis, differential diagnosis, and interpretation of laboratory tests, has become widespread (12-14). Additionally, as examined in our study, it is also commonly utilized for patient counseling services. However, providing accurate and reliable information is crucial for these models, especially within the medical field. Moreover, as LLMs improve in accuracy, they offer advantages such as early disease detection, more precise differential diagnoses, and potential reductions in healthcare costs. Several studies in the literature assess ChatGPT's diagnostic evaluation capabilities.

In a study by Krusche et al., ChatGPT was compared with rheumatologists in differentiating inflammatory rheumatic diseases (IRDs) from other conditions. ChatGPT-4 was found capable of providing accurate differential diagnoses, achieving better sensitivity than a rheumatologist in identifying IRDs, underscoring its high potential as a tool for IRD differential diagnosis (15). Another study evaluated ChatGPT's accuracy and adequacy in answering rheumatology questions on a specialized medical entrance examination, demonstrating its value as a tool in rheumatology education with a 93.71% accuracy score (16). ChatGPT has set a new standard for both healthcare providers and patients seeking medical information. In one study, ChatGPT's ability to appropriately answer frequently asked questions about total hip arthroplasty was assessed, demonstrating its capability to provide evidence-based answers that were both effective and accessible to patients (17).

Consistent with numerous studies evaluating ChatGPT's performance in medical contexts, our study shows that ChatGPT displays high accuracy and adequacy in answering patients' most frequently asked questions. Parallel studies have highlighted limitations in ChatGPT's ability to provide detailed information on certain medical conditions. Carnino et al. evaluated ChatGPT's responses to questions from ear, nose, and throat patients in terms of accuracy, comprehensiveness, and bedside manner/empathy, pointing out limitations, especially in terms of accuracy and comprehensiveness (18). Another study demonstrated that ChatGPT falls short in managing special or highly specific cases, such as emergency urological cases (19). These results underscore the importance of thoroughly evaluating and critically assessing the information provided by ChatGPT.

ChatGPT's language comprehension and response abilities can vary depending on the language chosen, which may affect the accuracy and level of detail in its responses. Studies have examined how large language models are influenced by language selection, noting that reasoning and analytical abilities may be limited in certain languages (20). In a study by Yaslikaya and Kidi, ChatGPT's responses were evaluated in both Turkish and English for general information on breast cancer, treatment options, risks, and prevention. They observed that using English facilitated a clearer understanding of ChatGPT's answers (21). Similarly, in our study, we found that responses in English were more detailed and accurate than their Turkish counterparts (3.64 vs. 3.89 for Expert 1, 3.83 vs. 3.94 for Expert 2).

These findings indicate that ChatGPT's accuracy in addressing complex medical topics may diminish when used in languages other than English. A possible explanation for the variability in accuracy across languages lies in the underlying training data and model architecture. Since ChatGPT is primarily trained on English data, this may contribute to the higher accuracy observed in English responses compared to other languages. This suggests that, while ChatGPT may be a useful tool for preliminary information, caution is warranted when relying on non-English responses, especially in complex or sensitive medical fields such as rheumatology and maternal-fetal medicine.

The scoring discrepancies between Expert 1 (rheumatologist) and Expert 2 (perinatologist) also highlight the subjective nature of evaluating ChatGPT's responses. Although the scoring system provides a structured approach to assessing response quality, individual perspectives based on professional expertise inevitably influence the interpretation of adequacy and accuracy. Differences in scoring between the experts reflected their unique professional perspectives, with Expert 1 focusing on rheumatologic details and Expert 2 prioritizing aspects relevant to maternal-fetal health.

Our study offers important insights into the use of AI-based tools for patient education. Specifically, while ChatGPT's English responses in sensitive medical areas like pregnancy-related rheumatologic diseases are generally comprehensive, inconsistencies observed in its Turkish responses suggest that AI platforms may not yet fully replace human experts in providing reliable, linguistically sensitive medical guidance. This discrepancy raises concerns regarding health information equity, as patients who speak languages other than English may not receive the same level of accuracy or detail in AI-generated answers.

The limitations of our study should be acknowledged. We evaluated responses from ChatGPT's free version 3.5; therefore, results may vary in the paid or more advanced versions of the model. Additionally, while the questions were designed based on frequently asked questions related to rheumatic diseases in pregnancy, the phrasing of questions may vary significantly across users. Future research could investigate whether variations in question phrasing impact response accuracy or whether repeated questions lead to different answers. Despite efforts to maintain consistency, the subjective nature of scoring remains a factor influencing the interpretation of ChatGPT's performance.

In conclusion, while ChatGPT shows promise as a supplementary information source in the fields of rheumatology and maternal-fetal medicine, its limitations, particularly in languages other than English, should not be overlooked. Patients and healthcare professionals should proceed with an awareness of these potential shortcomings, ensuring that complex cases are verified by a healthcare provider. Further research is needed to assess the performance of future AI models across multiple languages and specialized medical domains.

Ethics declarations
This study did not involve human subjects and was therefore determined to be exempt from IRB review

Author Contributions
BOU and COU contributed to the conception and design of the study. BOU conducted the data collection and initial analysis. COU provided additional insights and critical revisions during the data analysis process. Both authors participated in the interpretation of results, drafting, and revising the manuscript. BOU prepared the initial draft, while COU reviewed and edited the final version. Both authors approved the final version of the manuscript for submission.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Evaluation of the effect of vaginal delivery on stress urinary incontinence and bladder neck mobility with trans perineal ultrasonography

Vajinal doğumun stres üriner inkontinans ve mesane boyun hareketliliğine etkisinin transperineal ultrasonografi ile değerlendirilmesi

Hüseyin Aytuğ AVŞAR[1], Ufuk ATLIHAN[2], Onur YAVUZ[3], Can ATA[4], Selçuk ERKILINÇ[5], Tevfik Berk BİLDACI[6]

[1]Buca Seyfi Demirsoy Training and Research Hospital, İzmir, Türkiye
[2]Private Karataş Hospital, İzmir, Türkiye
[3]Dokuz Eylul University School of Medicine, İzmir, Türkiye
[4]Buca Seyfi Demirsoy Training and Research Hospital, İzmir, Türkiye
[5]İzmir Democracy University Faculty of Medicine, Oncology Department, İzmir, Türkiye
[6]İzmir Democracy University Faculty of Medicine, Obstetrics and Gynecology Department, İzmir, Türkiye

ABSTRACT

Aim: In our study, we aimed to evaluate the effect of vaginal birth, which is known to increase the likelihood of stress urinary incontinence, on bladder neck motility.

Materials and Methods: In our study, 116 patients who gave birth in our hospital between January 2020 and May 2022 were evaluated retrospectively. The presence of stress urinary incontinence and transperineal ultrasonography data of all patients were examined from the patient files. To evaluate changes in bladder neck motility, ultrasound measurements made both prenatally and postnatally were evaluated retrospectively.

Results: The presence of stress urinary incontinence was found to be statistically higher in the multiparous and primiparous patient groups compared to the patients in the cesarean section group. ΔDx, ΔDy and M values of the cesarean birth group were found to be significantly lower than both the primiparous and multiparous vaginal birth groups.

Conclusion: Vaginal birth was found to be a risk factor for stress urinary incontinence by increasing bladder neck mobility compared to cesarean delivery.

Keywords: Bladder neck mobility, perineal ultrasound, stress urinary incontinence, vaginal delivery

ÖZ

Amaç: Çalışmamızda, stres üriner inkontinans olasılığını arttırdığı bilinen vajinal doğumun mesane boynu hareketliliği üzerindeki etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2020 - Mayıs 2022 tarihleri arasında hastanemizde doğum yapan 116 hasta retrospektif olarak değerlendirilmiştir. Tüm hastaların stres üriner inkontinans varlığı ve transperineal ultrasonografi verileri hasta dosyalarından incelenmiştir. Mesane boynu hareketliliğindeki değişiklikleri değerlendirmek için hem doğum öncesi hem de doğum sonrası dönemlerde yapılmış olan ultrason ölçümleri retrospektif değerlendirildi. Bulgular: Multipar ve primipar hasta grubunda, sezaryen grubundaki hastalar ile karşılaştırıldığında stres üriner inkontinans varlığı istatistiksel olarak daha yüksek saptandı. Sezaryen doğum grubunun ΔDx, ΔDy ve M değerleri hem primipar hem de multipar vajinal doğum gruplarına göre anlamlı olarak daha düşük saptandı.

Sonuç: Vajinal doğumun sezaryen doğum ile karşılaştırıldığında mesane boynu hareketliliğini artırarak stres üriner inkontinans için bir risk faktörü olduğu saptandı.

Anahtar Kelimeler: Mesane boynu hareketliliği, perineal ultrason, stres üriner inkontinans, vajinal doğum

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Sorumlu Yazar/Corresponding Author: Hüseyin Aytuğ AVŞAR, Buca Seyfi Demirsoy Training and Research Hospital, İzmir, Türkiye
E-mail: aytugavsar@hotmail.com

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INTRODUCTION

Urinary incontinence is a distressing and prevalent situation in females, impacting emotional and psychological well-being by interrupting sexual, physical, and social forms of life. Stress urinary incontinence (SUI) is defined by the involuntary release of urine during actions like sneezing, coughing, or physical activity, without bladder contraction (1). SUI arises when the natural interplay of anatomical and functional factors is disturbed. Two mechanisms elucidate SUI: intrinsic sphincter and urethral hypermobility deficiency. Perineal trauma, especially during childbirth, is one of the most common contributing factors (2-5). Differentiating between urethral malposition or hypermobility and intrinsic sphincter deficit (ISD) is a common method used to classify SUI, yet this may be oversimplifying the situation (6). According to the McGuire categorization system, urethral hypermobility causes stress incontinence in types 1 and 2, whereas intrinsic sphincter deficit causes type 3 of stress incontinence (7). It is known that SUI negatively affects the life quality in 54.3% of all pregnant females in four areas: emotional health, social relations, travel, and physical activity. Sangsawang et al. reported that lower urinary tract symptoms most frequently occur in the 36th week of pregnancy and continue one year after pregnancy (8). One of the primary causes of neuromuscular injury in the pelvic floor is trauma sustained during birth (9). In terms of delivery method, according to ultrasound examination, vaginal birth results in more damage to the pelvic floor than cesarean section since it is correlated with a higher incidence of levator ani muscle injuries, puborectalis deformities, increased neck mobility of the bladder, and expansion of the hiatal region (10). Pelvic floor ultrasound is gaining popularity in urogynecology. Studies have demonstrated good reproducibility of ultrasonographic measurements of pelvic structures (11). Dietz et al. found that perineal ultrasound evaluation of bladder neck motility using a transabdominal probe remained consistent, even when repeated after several weeks (12). Ultrasound assessments of urethral mobility offer a direct visualization of bladder neck mobility, which correlates with the severity of stress urinary incontinence. Pelvic floor ultrasound offers several advantages over other diagnostic methods for stress urinary incontinence, including affordability, noninvasiveness, real-time imaging capabilities, and the ability to repeat measurements multiple times. The objective of this research is to evaluate the impact of vaginal delivery, a known risk factor for postpartum stress incontinence, on bladder neck mobility. This will be accomplished using transperineal ultrasonography, a diagnostic method that is noninvasive and well-tolerated.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at a tertiary center. Informed consent forms were obtained from participants for the current study. The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. This study was started after receiving ethics committee approval from our hospital dated 25/10/23 and numbered 2023/177. In our study, 116 pregnant women who were followed up in our gynecology outpatient clinic from January 2020 to May 2022 and whose deliveries were made in a tertiary care hospital were included. This study included 50 primiparous patients and 66 patients who had experienced one or more deliveries (multiparous). Initial transperineal ultrasonography assessments were conducted between the 32nd and 36th weeks of gestation, and subsequently, during the 6th week postpartum. Retrospective data collection was done using patient files and the hospital database. To ensure participant homogeneity, individuals with complicated deliveries involving forceps and vacuum extraction, those experiencing pregnancy complications (multiple pregnancies, macrosomia, intrauterine growth restriction), those with a urinary tract infection during pregnancy, with a history of normal birth after cesarean section, and those with a history of gynecological or incontinence surgery were not included in the research.

The study group consisted of females who delivered vaginally with fetuses in the vertex presentation, while the control group was formed from individuals who delivered through selective cesarean section. The participants were categorized into three groups: (1) group of primiparous vaginal delivery, (2) group of multiparous vaginal delivery, and (3) group of elective cesarean section. Postnatal assessment encompasses the method of delivery, the need for episiotomy in vaginal delivery, the duration of the 2nd stage of labor, and the baby's birth weight. The time limits for diagnosing failure to progress at the 2nd stage of labor were determined as two hours for nulliparous females and one hour for multiparous females, based on the criteria established by ACOG in 1989. Incontinence was assessed by questioning patients twice, during the 32-36th gestational weeks and at the 6th postnatal week. The Ingelmann Sundberg classification was used to grade incontinence.

1st Degree: Urinary incontinence during coughing, sneezing, and laughing.

2nd Degree: Urinary incontinence while walking, running, climbing, and jumping.

Perineal ultrasonography examinations were conducted using a Samsung SonoaceR7 and a 3.5 MHz convex probe, within a bladder volume ranging from 100 to 300 ml. This allowed visualization of

the bladder base and neck, urethra, and symphysis pubis through transsagittal imaging. Examination of the bladder neck involved assessing its position relative to an anatomical landmark, the lower border of the pubic symphysis. Initially, the lower edge of the symphysis pubis, bladder, urethrovesical junction, and urethra at rest were imaged and the image was frozen on one side of the screen. Subsequently, patients were imaged during the Valsalva maneuver, with the resulting image frozen and located on the other half of the screen. Analysis of bladder neck position was conducted using the XY coordinate system, a reproducible technique where the X-axis was a vertical line tangent to the lower border of the symphysis pubis, and the Y-axis was perpendicular to the X-axis. Standardization of scenario and image acquisition ensured consistency across patients, with the transducer positioned on top and the patient's ventral aspect represented on the left side of the screen. At rest, the distance between the bladder neck and the Y-axis is defined as Dyr, and at the time of the Valsalva maneuver, Dyv. The same applies to the X-axis as Dxr and Dxv. Subtraction scores of Dyv and Dyr indicated bladder neck cephalocaudal mobility (ΔDy). Subtraction scores of Dxr and Dxy indicated bladder neck ventrodorsal mobility (ΔDx). Bladder neck mobility was determined as vector distance with the following formula: Mobility (M) = $\sqrt{}$ (xv-xr) ² + (yr-yv)². Vector distance was compared after and before delivery for every participant. Prenatal values (ΔDx1, ΔDy1, M1) were defined as postnatal values (ΔDx2, ΔDy2, M2). Subtraction values of postnatal measurements and prenatal measurements differed. Participants were urged to refrain from exercising their pelvic floor muscles until the 6th week after delivery.

Statistical analysis was performed by SPSS version 26.0 (IBM Inc., Chicago, IL, USA). The distribution normality was evaluated with Kolmogorov-Smirnov test. Normally distributed parameters were analyzed by using ANOVA. Not normally distributed parameters were analyzed by using the Kruskal Wallis and Mann-Whitney U tests. Chi-square test and Fisher precision test were utilized in the analysis of categorical data. Quantitative data with normal distribution are shown as mean ± SD, while quantitative data with non-normal distribution are shown as median (min-max). Descriptive statistics of categorical data are presented as number (n) and percentage (%). A p-value smaller than 0.05 was taken statistically significant.

RESULTS

With regard to the demographic values of the patients, a statistically significant difference was seen in terms of the presence of urinary incontinence when multiparous and primiparous patients were compared with patients in the cesarean section group (p:0.01). There were 36 (72%) patients with a history of cesarean section once, and 14 (28%) patients with a history of cesarean section twice. There was no statistically significant difference between the groups regarding birth weight, body mass index (BMI), age, and ultrasound week (Table 1).

In the antepartum period, ΔDx, ΔDy values of the cesarean section group showed significant differences compared to both primiparous and multiparous vaginal birth groups (p:0.04, p:0.04, respectively). There was a significant difference in the M value of the cesarean birth group compared to both the primiparous and multiparous vaginal birth groups (p:0.02). In the postpartum period, ΔDx, ΔDy values of the cesarean section group showed significant differences compared to both primiparous and multiparous vaginal birth groups (p:0.03, p:0.04, respectively). There was a significant difference in the M value of the cesarean birth group compared to both the primiparous and multiparous vaginal birth groups (p:0.02) (Table 2).

Table 1. Comparative Analysis of Demographic Characteristics Across Varied Delivery Modes

	Normal Spontaneous Vaginal Delivery		C/S	p
	Primiparous	Multiparous		
	Mean±SD			
Age (year)	27.18 ±4.39	27.67 ± 4.63	27.11 ± 4.89	0.08
BMI (kg/m²)	24.19 ± 4.59	24.61 ± 5.11	24.26 ± 4.77	0.09
Parity	1.00 ± 0.00	2.21 ± 0.84	1.00 ± 0.00	**0.01**
Birth Weight (g)	3345.9 ± 592.7	3380.4 ± 484.6	3311.1 ± 550.6	0.07
Ultrasound Week	35.74 ± 1.37	35.55 ± 1.19	35.85 ± 1.29	0.09

*BMI: Body mass index, C/S: Cesarean Section

Table 2. Assessment of antepartum and postpartum Ultrasonographic Parameters Based on Delivery Modes

	Antepartum			p	Postpartum			p
	Primiparous	Multiparous	C/S		Primiparous	Multiparous	C/S	
ΔDx (mm)	7.26±0.59	8.12±2.62	5.66±2.01	**0.04**	8.38±0.63	9.98±2.52	5.86±1.27	**0.03**
ΔDy (mm)	15.43±1.18	17.01±2.66	11.66±2.56	**0.04**	16.84±1.26	18.24±2.95	11.72±2.88	**0.04**
M (mm)	17.03±0.89	18.22±2.88	12.99±2.58	**0.02**	18.53±0.84	20.12±3.29	12.92±2.87	**0.02**

* C/S: Cesarean section

Table 3. Evaluation of Ultrasound Parameters According to the Type of Birth

	Primiparous n:20	Multiparous n:46	C/S n:50	p
ΔDx difference	1.12±1.03	1.86±2.22	0.20 ±1.22	0.016
ΔDy difference	1.39±1.58	1.23±0.86	0.06±0.88	0.018
M difference	1.50±1.49	1.90±0.92	-0.07±0.86	0.022

* C/S: Cesarean section

Table 4. Postpartum Incontinence Evaluation According to the Presence of Episiotomy

		Episiotomy		p
		(+) n:30	(-) n:36	
Primiparous n:20	SUI (+)	5 (33.3%)	5 (100%)	**0.02**
	SUI (-)	10 (66.7%)	0 (0%)	
Multiparous n:46	SUI (+)	9 (60%)	19 (61.2%)	0.9
	SUI (-)	6 (40%)	12 (38.8%)	

*SUI: Stress urinary incontinence

The ΔDx difference and ΔDy difference between antepartum and postpartum were found to be statistically significantly lower in the cesarean section group compared to the primiparous vaginal birth group and multiparous vaginal birth group (p:0.016 and p:0.018, respectively)

The M difference between antepartum and postpartum were found to be statistically significantly lower in the cesarean section group compared to the primiparous vaginal birth group and multiparous vaginal birth group (p:0.022) (Table 3).

When evaluating primiparous and multiparous patients individually for symptoms of SUI at 6 weeks postpartum, it was observed that in the primiparous group, patients delivered without episiotomy were significantly more likely to experience SUI than those without (p:0.02). In the multiparous group, no significant difference was noted based on the presence or absence of episiotomy (p:0.9) (Table 4).

In the group of patients with SUI symptoms postpartum, a significant difference was found between prenatal and postnatal measurements of bladder neck mobility. Vectorial, ventrodorsal, and cephalocaudal movements were found to be significantly greater than group of patients does not present SUI symptoms ($p < 0.05$) (Table 5).

DISCUSSION

In our study, stress urinary incontinence values at pregnancy were seen to be similar to the primiparous patient group and lower than the multiparous patient group. This suggests that

Table 5. Assessment of Antepartum and Postpartum Ultrasonographic Parameters Based on the Presence of Incontinence Symptoms

		Postpartum SUI Symptoms (+) n: 49	Postpartum SUI Symptoms (-) n:67	p
Antepartum	ΔDx(mm)	7.92 ± 2.32	5.79 ± 1.76	**0.03**
	ΔDy(mm)	15.84 ± 2.76	11.90 ± 2.11	**0.04**
	M(mm)	17.68 ± 2.88	13.16 ± 2.12	**0.03**
Postpartum	ΔDx(mm)	9.68 ± 2.29	5.99 ± 1.18	**0.01**
	ΔDy(mm)	17.77 ± 2.65	11.95 ± 2.52	**0.02**
	M(mm)	19.66 ± 3.03	13.32 ± 2.67	**0.02**

*SUI: Stress urinary incontinence

pregnancy alone may be one contributing factor to pelvic muscle dysfunction. Two different studies identified a history of cesarean section as a pregnancy-related risk factor for urine incontinence (13, 14). Groutz et al. showed that the occurrence of postpartum stress urinary incontinence was comparable between spontaneous vaginal delivery and cesarean section after non-progressed labor. In such instances, it's plausible that pelvic floor damage may already be too extensive to be prevented by surgical intervention. However, elective cesarean section in the absence of prior labor history was linked with a notably lower prevalence of stress urinary incontinence (15). In another research by Nygaard et al., it was stated that females who had their second vaginal delivery experienced urinary incontinence problems twice as often as those who gave birth by cesarean section (16).

The pudendal nerve may sustain injury during delivery as a result of tugging or compression in the Alcock canal. Snooks et al. described denervation after vaginal delivery that lasted for two months after delivery utilizing single fiber EMG of the pudendal nerve latency and external anal sphincter (17). Additionally, aberrant collagen patterning or hormonal changes during pregnancy may potentially have a significant role in the development of postpartum SUI (18). In the postpartum period, the incidence of SUI in patients with a history of cesarean section was significantly lower than in the primiparous and multiparous vaginal delivery patient groups. Additionally, elective cesarean section was associated with a lesser rise in bladder neck mobility in comparison with primiparous and multiparous patients with vaginal delivery. This can be interpreted as cesarean delivery serving as a protective measure against the development of SUI.

Transperineal ultrasonography enables repeatable quantitative measures by allowing for the morphological and dynamic evaluation of the bladder neck and urethra. It is possible to measure the location of the bladder neck both at rest and during the maximum Valsalva movement. The discrepancies between the two measurements may be used to calculate the bladder neck displacement. Measurements of the bladder neck position are taken both at rest and during the maximum Valsalva movement. Proximal urethra displacement in a posteroinferior orientation is possible in Valsalva. Despite the suggestion of cutoffs between 15 and 25 mm to characterize hypermobility, bladder neck displacement lacks a "specific definition of normal" (19, 20). In our study, to be able to get great precision, we used a bidirectional XY coordinate system. Cephalocaudal and ventrodorsal mobility were found to be significantly higher in both the primiparous and multiparous groups that delivered vaginally compared to the elective cesarean section group. A study has demonstrated that vaginal delivery causes pelvic floor damage and disrupts innervation (21). In our study, bladder neck mobility in the multiparous and primiparous groups was significantly higher than in the cesarean section group, supporting the findings of our study. It is reported in the literature that the incidence and severity of incontinence increase as pregnancy progresses, especially at its climax in the third trimester (22, 23). For this reason, we took measurements at 32-36th gestational weeks.

Both antepartum and postpartum vector bladder neck movement measurements were higher in patients presenting symptoms of SUI than in patients not presenting symptoms in the postpartum period. Contrary to our study, one study reported that both the continent and incontinent groups showed a comparable increase in bladder neck mobility following delivery beyond antepartum values, indicating that the incontinent group did not experience more tissue stress from birth. However, in that study, they stated that the development of SUI cannot be explained solely by the obstetric experience of female (24).

A study has shown that women with more than four vaginal deliveries have significantly higher rates of urinary incontinence. This study supports the idea that pelvic floor damage increases

exponentially with the number of vaginal deliveries (25). Despite the belief that vaginal birth harms the shape and functionality of the pelvic organs, according to several writers' incontinence usually decreases significantly after 6 weeks and usually disappears within three months after delivery (23, 26). Also, transient incontinence during pregnancy is suggested to be a result of the interaction between predisposing hereditary factors, the pressure of the uterus on the bladder, and hormonal effects on the suspensory ligaments of the urethra (27). Unlike Wilson PD et al. (25), who used not only SUI but a broad definition for urinary incontinence to evaluate patients at postpartum 3 months, this could be a reason for our results conflicting with their study. The study had some limitations. One of these was that the study was retrospective. For this reason, patients whose data were not recorded or who did not come for a postpartum control were excluded from the study. This situation caused the small number of patients, which is another limitation. The results could have been more remarkable in a study conducted on a larger population. The strength of the study could be considered as the fact that the imaging method applied can be performed routinely, is easily accessible, and does not impose any additional costs on the patient.

CONCLUSION

Vaginal birth was found to be a risk factor for stress urinary incontinence by increasing bladder neck mobility compared to cesarean delivery. Transperineal ultrasound seems to be a suitable method for assessing bladder neck mobility. This technique can aid in identifying urinary incontinence during and after pregnancy.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Platelet transfusion as a risk factor for development retinopathy of prematurity

Prematüre retinopatisi gelişimi için bir risk faktörü olarak trombosit transfüzyonu

Duygu TUNÇEL[1], Sevdet BALIK[2], Leyla ŞERO[2], Dilbade Yıldız EKİNCİ[3], Nilüfer OKUR[1]

[1]SBU Gazi Yasargil Training and Research Hospital, Department of Pediatrics, Division of Neonatology, Diyarbakır, Türkiye
[2]SBU Gazi Yasargil Training and Research Hospital, Department of Pediatrics, , Diyarbakır, Türkiye
[3]SBU Gazi Yasargil Training and Research Hospital, Department of Opthalmology Diyarbakır, Türkiye

ABSTRACT

Aim: The aim of this study was to determine the potential association between platelet transfusions and the development of retinopathy of prematurity.

Materials and Methods: This was a retrospective, cross-sectional, case-control study. Premature infants with gestational age <32 weeks were divided into two groups: those who developed severe retinopathy of prematurity (ROP) (Stage >2) and those who did not. Demographic data, short- and medium-term morbidities, presence of transfusion and number of transfusions were recorded from the hospital data system and patient files. Conditional logistic regression analysis was performed to adjust for matching.

Results: A total of 130 premature infants were included in the study between January 2017 and January 2021. Severe ROP was detected in 80 (61.5%) of the patients. Birth weights in the groups with and without severe ROP were 1201±256 g and 1035±341 g (p=0.03), and gestational ages were 28.6±2 weeks and 27.5±2 weeks (p=0.06), respectively. Twenty-one patients received platelet transfusion. The number of platelet transfusions was higher in the severe ROP group (p<0.01). There was a significant correlation between the number of platelet transfusions and the need for ROP treatment (-0.21, p=0.016).

Conclusion: There was a significant correlation between the number of platelet transfusions and the development of retinopathy requiring treatment. Further prospective randomised controlled trials are needed to establish a link between platelet transfusions and the development of severe retinopathy of prematurity.

Keywords: Platelet transfusion, prematurity, retinopathy

ÖZ

Amaç: Bu çalışmanın amacı trombosit transfüzyonları ile prematüre retinopati gelişimi arasındaki potansiyel ilişkiyi belirlemektir.

Gereç ve Yöntemler: Bu retrospektif, kesitsel, vaka-kontrol çalışmasıdır. Gebelik yaşı <32 hafta olan prematüre bebekler, ciddi prematüre retinopatisi (ROP) gelişen (Evre >2) ve gelişmeyenler olarak iki gruba ayrılmıştır. Demografik veriler, kısa ve orta vadeli morbiditeler, transfüzyon varlığı ve transfüzyon sayıları hastane veri sisteminden ve hasta dosyalarından kaydedildi. Eşleştirmeyi ayarlamak için koşullu lojistik regresyon analizi yapıldı.

Bulgular: Ocak 2017 ve Ocak 2021 tarihleri arasında toplam 130 prematüre bebek çalışmaya dahil edildi. Hastaların 80'inde (%61,5) ciddi ROP saptandı. Ciddi ROP olan ve olmayan gruplarda doğum ağırlıkları sırasıyla 1201±256 g ve 1035±341 g (p=0.03), gebelik yaşları 28.6±2 hafta ve 27.5±2 hafta (p=0.06) idi. Yirmi bir hastaya trombosit transfüzyonu yapıldı. Trombosit transfüzyonu sayısı ciddi ROP grubunda daha fazlaydı (p<0.01). Trombosit transfüzyonu sayısı ile ROP tedavi ihtiyacı arasında anlamlı bir korelasyon vardı (-0.21, p=0.016).

Sonuç: Trombosit transfüzyonu sayısı ile tedavi gerektiren retinopati gelişimi arasında anlamlı bir ilişki bulunmuştur. Ciddi prematüre retinopatisi gelişimi ile trombosit transfüzyonları arasında bir bağlantı kurmak için daha fazla prospektif randomize kontrollü çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Trombosit transfüzyonu, prematürite, retinopati

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Sorumlu Yazar/Corresponding Author: Duygu TUNÇEL, SBU Gazi Yasargil Training and Research Hospital Department of Neonatology, Istanbul, Türkiye
E-mail: tncldyg@yahoo.com

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INTRODUCTION

Retinopathy of prematurity (ROP) is the leading cause of ocular morbidity in premature infants and is also the most common preventable cause of visual impairment in childhood (2). The prevalence of ROP varies worldwide, with approximately 60% observed in extremely low birth weight infants (1). However, studies have reported higher ROP rates in both extremely low birth weight infants and infants weighing over 1500 grams and born at 28 weeks or more, particularly in underdeveloped and developing countries (2).

Retinopathy is closely associated with low birth weight, gestational age, and hyperoxia (3). Premature infants often require blood product transfusions during their stay in the neonatal intensive care unit. Blood transfusions can have adverse effects on infants. While allergic and hematological side effects are frequently discussed, recent years have seen an understanding that blood product transfusions increase the release of vascular endothelial growth factor (VEGF), other cytokines, and inflammatory modulators, possibly leading to an inflamed state. Considering the pathophysiology of retinopathy, this inflammatory process, particularly the potential of increased VEGF release in the developing retina, may trigger the development of new blood vessels and consequently contribute to the development of ROP (1,2). There is evidence in the literature suggesting that erythrocyte transfusions can increase the risk of ROP, as transfusion of adult erythrocytes to premature infants leads to decreased fetal hemoglobin levels. Elevated oxygen affinity of adult hemoglobin in the retina can increase hyperoxic conditions, potentially triggering the development of severe ROP (2,5). Platelet transfusions in premature infants are also controversial due to their pro-inflammatory and anti-angiogenic properties (4).

While ROP remains a significant concern, identifying associated factors and improving outcomes are crucial. The objective of this study is to investigate the relationship between platelet transfusion and the development of ROP.

MATERIALS AND METHODS

This retrospective study included 130 premature infants with a gestational age of less than 32 weeks who were born in the third-level neonatal intensive care unit (NICU) between January 2017 and January 2021. Ethical approval of the study was obtained from the local ethics committee (26.05.2023/419). All premature babies born in our centre with a gestational age less than 32 weeks and followed up for retinopathy of prematurity were included in the study. Infants with major congenital anomalies, asphyxia, intrauterine infections, missing data in hospital records and those who were lost before their first retinopathy examination were excluded. Patients were divided into two groups as severe ROP and ROP not requiring treatment according to the 'Turkey Retinopathy of Prematurity Guideline 2021 update' of Turkish Neonatology Society and Turkish Ophthalmological Society. Severe ROP was defined as Type 1 ROP ('plus' disease at any stage in Zone I, stage 3 ROP in Zone I, stage 2 or stage 3 ROP and 'plus' disease in Zone II) and Aggressive-ROP was defined as severe ROP requiring treatment (6). Both groups were compared in terms of demographic data. The incidence of respiratory distress syndrome (RDS), haemodynamically significant patent ductus arteriosus (hsPDA), stage 2-3 according to modified Bell staging necrotizing enterocolitis (NEC), Stage 3 intraventricular haemorrhage (IVH)/periventricular haemorrhagic infact according to Volpe staging and severe bronchopulmonary dysplasia (BPD) was evaluated. In our clinic, platelet transfusions are performed according to the threshold values recommended by the Turkish Neonatology Society: Platelet count <25.000/μL; all infants, neonatal alloimmune thrombocytopenia, 25.000/-49.000/μL; birth weight <1000 grams, coagulopathy, severe morbidity, invasive intervention, minor bleeding, 50.000-100.000/μL; active or major bleeding, disseminated intravascular coagulopathy, perioperative, >100.000/μL; major surgery (7). Erythrocyte trasfusions are also performed in accordance with the recommendations of the same guideline Erythrocyte transfusion was performed on premature infants based on their post-conceptional age and respiratory support status, targeting hemoglobin values according to age or providing 15-20 ml/kg of erythrocyte suspension in cases of tachycardia, increased oxygen support, or poor weight gain. (7). The numbers of erythrocyte and platelet transfusions were recorded retrospectively from hospital records. Erythrocyte and platelet transfusions were performed according to the transfusion recommendations of the guidelines and administered to infants at a dose of 10-15 ml/kg (7).

Statistical Analysis

Statistical analyses were conducted using the SPSS statistical software for Windows, V.21.0 (SPSS, Chicago, Illinois, USA). The Shapiro–Wilk test was used to test for the normality of data. Chi-square or Fisher's exact test was used for comparison of categorical variables as appropriate. Differences between the groups concerning continuous variables were compared by Student's t test and Wilcoxon test where appropriate. A p value of <0.05 was considered statistically significant. Conditional logistic regression analysis was conducted to determine the relationship between transfusions and severe ROP development and to assess all potential risk factors.

RESULTS

A total of 130 premature infants were included in the study between 1 May 2023 and 1 June 2023. Eighty (61.5%) infants were followed up with the diagnosis of severe ROP and 50 (38.5%) infants were followed up with the diagnosis of ROP not requiring treatment. Birth weights were 1035±341 and 1201±256 g (p=0.03) and gestational ages were 27.5±2 and 28.6±2 weeks (p=0.06) in the severe ROP and treatment-naive ROP groups, respectively. There was a significant difference in terms of mechanical ventilation and length of hospital stay between the severe ROP and treatment-free ROP groups (p<0.05). The incidence of respiratory distress syndrome, patent ductus arteriosus, intracranial haemorrhage, necrotising enterocolitis and other short-term morbidities were similar in both groups (p>0.05). Total oxygen duration was significantly associated with the development of severe ROP group (p<0.05). No significant difference was observed between the two groups in terms of early and late neonatal sepsis (p=0.41) (Table 1). Red cell transfusion was performed in 76 patients. Red cell transfusion was performed in 54% of patients with severe ROP and 22% of patients with ROP not requiring treatment, and this rate was higher in patients with severe ROP (Table 2). A total of 21 patients received platelet transfusions. The number of platelet transfusions was higher in the severe ROP group (p<0.01). There was a positive correlation between the number of platelet transfusions and the need for ROP treatment. The transfusion volume in the severe ROP group was 28±8 mg/kg, which was higher than the ROP group that did not require treatment (p=0.042) (Table 2). Linear regression analysis of some parameters associated with the development of ROP showed that platelet transfusion was associated with the development of severe ROP (Table 3).

Table 1. Clinical findings and releated complications of the patients

	Low stage ROP (N=50)	Severe ROP (N=80)	p
Gestational age,week*	28,6±2	27.5±2	**0.06**
Birthweight, g*	1201±256	1035±341	**0.03**
Male/female, n	25/26	42/38	0,49
Sepsis, n (%)	23 (46)	42 (52)	0,41
Severe IVH, n (%)	6 (12)	14 (17.5)	0,26
NEC, n (%)	1 (2)	8 (16)	0,076
RDS, n (%)	41 (82)	73 (91)	0,064
Severe BPD, n (%)	11 (22)	30 (37.5)	**0,041**
hsPDA, n (%)	33 (66)	44 (55)	0,179
Surfactant, n (%)	37 (74)	61 (76.3)	0,39
Phototherapy, n (%)	43 (85)	35 (43.8)	0,36
Apgar, 5. minute**	7 (1-10)	6 (2-9)	**<0,01**
Duration of hospitalisation (day)*	46±23	75±44	**<0,01**
Duration of invasive mechanic ventilation (day)**	13±2,8	38±4,7	**<0,01**
Duration of total oxygen therapy (day)*	30 ±3,6	62 ±5,1	**0,04**

* Mean±Standart deviation **Median (minimum-maximum)

Table 2. Comparison of transfusions in severe ROP and ROP not requiring treatment groups

	Low stage ROP (N:50)	Severe ROP (N:80)	P value
Platelet transfusion, n (%)	2 (4)	21 (26)	**<0,01**
Red blood cell transfusion, n (%)	22 (44)	54 (67.5)	**<0,005**
Platelet transfusion volume, mL/kg *	15±5	28±8	**0.042**

*Mean±Standart deviation

Table 3. Logistic regression analysis of the variables

	B	S.E.	Sig.	Exp(B)
Platelet transfusion	-1,781	,855	,034	,169
Red blood cell transfusion	-,615	,606	,310	,541
Birthweight, g	-,568	,001	,050	1,000
Gestational age,week	-,500	,109	,017	,931

DISCUSSION

Partial oxygen pressures are higher in the postnatal period compared to the intrauterine period. Hyperoxia suppresses VEGF, thus retinal vascularisation is delayed. The metabolically active retina gradually becomes more and more hypoxic and abnormal

vascularisation is caused by an increase in VEGF and other pro-angiogenic factors. the most known risk factors are low birth weight and gestational age (8). Hyperoxia (8) and sepsis (9) are also reported to be serious risk factors. Studies have shown that erythrocyte and platelet transfusions have some side effects, such as the release of proinflammatory and immunomodulatory mediators such as VEGF (10).

In this study, we found a significant relationship between platelet transfusion and the development of ROP.

Infants requiring transfusion are not only premature but also critically ill. These patients are at higher risk of neonatal complications due to maternal diseases, prolonged mechanical ventilation due to respiratory distress, and delayed initiation of breastfeeding, all of which can increase the incidence of sepsis. While the presence of sepsis, a known risk factor for ROP, was similar in our patient groups, especially late neonatal sepsis is one of the common causes of neonatal thrombocytopenia in hospitalized premature infants (11). Thrombocytopenia itself increases mortality and morbidity in these patients. The relationship between thrombocytopenia and retinopathy is another area of investigation. Some studies have shown an association between thrombocytopenia and the development of ROP (12-15).

Blood product transfusions come with certain side effects. Considering the pathophysiology of retinopathy, it is known that platelets induce pro-inflammatory and anti-angiogenic reactions (4). Platelet transfusion releases cytokines, VEGF, and other immunomodulatory mediators, supporting inflammatory and proliferative processes (2,12,16). Consistent with the literature, our study also found an increased incidence of severe retinopathy in infants who received platelet transfusions. Therefore, careful consideration should be given to pre-transfusion decisions, particularly in premature infants with inadequate anti-inflammatory and antioxidant responses. Adherence to recommended indications for platelet transfusion in guidelines is essential. Hengartner et al (17) reported that patients who received 1 or more platelet transfusions had a higher risk of developing ROP (39% vs. 18%, $p < 0.001$, $r = 0.23$), but there was no difference between the groups in terms of the number of transfusions per infant, transfusion volumes and timing of transfusions. However, in our study, high platelet volume was also associated with the development of severe ROP, probably because the number of platelet transfusions was low in the untreated ROP group.

The relationship between erythrocyte transfusions and the development of ROP can be better understood when compared to platelet transfusions. The presence of adult hemoglobin leads to hyperoxic conditions in the retina, negatively impacting retinal neovascularization and thus increasing the risk of ROP (14). In our study, a significant association was found between the number of erythrocyte transfusions and the development of severe retinopathy. However, since anaemia frequently develops in premature infants, erythrocyte transfusions were frequently performed in both groups and no association was found with the development of severe ROP in logistic regression analysis.

Although the study includes patients from a single center, ensuring standardized transfusion quantities, there are limitations. It is important to note that our study is observational, so we can not definitively establish a causal relationship between platelet transfusion and ROP. More randomized controlled trials, are needed to confirm these findings. Other limitation is days of initial transfusion were not recorded. The postnatal days requiring platelet transfusion in relation to the stages of retinopathy could also influence the severity of retinopathy.

In conclusion, we identified a significant relationship between platelet transfusion and the development of severe retinopathy. However, more randomized controlled trials are necessary to definitively establish platelet transfusion as a risk factor in the etiology of premature retinopathy.

Disclosure statement:
The authors report there are no competing interests to declare.

İnformed consent:
Verbal consent was obteined from the families of patients included in the study.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Can the Delta Neutrophil Index (DNI) be used as a marker to predict whether the ovaries are viable or not in cases of ovarian torsion before surgery?

Delta Nötrofil İndeks (DNI), over torsiyonu olgularında cerrahi öncesinde over canlılığını tahmin etmek için bir belirteç olarak kullanılabilir mi?

Gamze YILMAZ[1], Hatice AKKAYA[2]

[1]Republic of Türkiye Ministry of Health, Ankara City Hospital Department of Obstetrics and Gynecology, Türkiye
[2]University of Health Sciences, Ministry of Health Ankara City Hospital, Department of Obstetrics and Gynaecology, Türkiye

ABSTRACT

Aim: To assess the predictive capability of the preoperative Delta Neutrophil Index (DNI) value in deciding whether to pursue an ovarian-preserving approach.

Materials and Methods: This retrospective cohort study was conducted on 81 women diagnosed with ovarian torsion. All patients underwent surgery, with 48 undergoing surgical detorsion and 33 undergoing oophorectomy. The latter group had available final pathology results. Patients were categorized based on final pathology results into groups with and without necrosis. None of the detorsion patients required reoperation within the first month. Surgery type , number of ovarian twists, preoperative admission hemogram parameters and final histological diagnosis were recorded, and it was evaluated whether the DNI values could be used as a predictive marker of ovarian viability in cases of ovarian torsion.

Results: A DNI value cut-off of 0.70 yielded 95.7% specificity, 83.3% sensitivity, 97.1% negative predictive value, and 83.3% positive predictive value for predicting necrosis. For neutrophil to lymphocyte ratio (NLR) values, a cut-off of 7.53 resulted in 77% specificity, 91.7% sensitivity, 98% negative predictive value, and 39% positive predictive value for predicting necrosis. No significant association was observed between necrosis and ovarian enlargement, the duration of time between the initial onset of pain and surgery, or the number of adnexal twists. However, the necrosis group exhibited significantly higher leukocyte counts, especially neutrophil counts($p<0.01$).

Conclusion: Our study suggests that having DNI and NLR values lower than the preoperative total blood count cut-off levels may serve as valuable guidance to surgeons in assessing the absence of ovarian necrosis.

Keywords: Ovarian torsion, delta neutrophil index, necrosis

ÖZ

Amaç: Delta Nötrofil İndeksi'nin (DNI), cerrahi öncesinde overlerin canlılığını tahmin etmedeki etkinliğini değerlendirmek ve over koruyucu cerrahi yaklaşımları desteklemedeki rolünü incelemek.

Gereç ve Yöntemler: Bu retrospektif kohort çalışması, over torsiyonu tanısı konmuş 81 kadın üzerinde gerçekleştirildi. Hastaların 48'ine cerrahi detorsiyon, 33'üne ise ooferektomi yapıldı ve ooferektomi grubunda nihai patoloji sonuçları incelendi. Hastalar, patoloji sonuçlarına göre nekroz olan ve olmayan olarak iki gruba ayrıldı. Detorsiyon uygulanan hiçbir hasta, ilk ay içinde yeniden cerrahiye ihtiyaç duymadı. Çalışmada, cerrahi türü (detorsiyon veya ooferektomi), torsiyon sayısı, cerrahi öncesi tam kan parametreleri ve nihai histopatolojik sonuçlar kaydedildi. DNI'nin, over torsiyonu durumlarında overlerin canlılığını öngörmek için kullanılıp kullanılamayacağı değerlendirildi.

Bulgular: DNI için belirlenen 0.70 eşik değerin, nekroz tahmininde; %95,7 özgüllük, %83,3 duyarlılık, %97,1 negatif prediktif değer ve %83,3 pozitif prediktif değer sağladığı belirlendi. Nötrofil-lenfosit oranı (NLR) için belirlenen 7.53 eşik değeri ise %77 özgüllük, %91,7 duyarlılık, %98 negatif prediktif değer ve %39 pozitif prediktif değer gösterdi. Nekroz ile over boyutu, ağrının başlangıcından cerrahiye kadar geçen süre veya torsiyone tur sayısı arasında anlamlı bir ilişki bulunmadı. Bununla birlikte, nekroz grubunda lökosit ve özellikle nötrofil sayıları anlamlı derecede yüksek bulundu ($p < 0.01$).

Sonuç: Bu çalışma, cerrahi öncesi DNI ve NLR değerlerinin belirlenen eşik değerlerin altında olması durumunda, over nekrozu bulunmadığını değerlendirme konusunda cerrahlara önemli bir yol gösterici olabileceğini ve over koruyucu cerrahi yaklaşımlara rehberlik edebileceğini ortaya koymaktadır.

Anahtar Kelimeler: Over torsiyonu, delta nötrofil indeks, nekroz

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Sorumlu Yazar/Corresponding Author: Gamze YILMAZ, University of Health Sciences, Ankara City Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye
E-mail: gamze_u@hotmail.com

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INTRODUCTION

Ovarian torsion is a gynecological emergent situation which has a 2.7% prevalence (1). Prompt diagnosis and urgent surgical intervention are required to avoid necrosis and serious consequences on ovarian function and subsequent fertility (2-4). But diagnosis is often difficult. The most common presentation is lower abdominal pain, with other associated symptoms including nausea, vomiting and fever (5). The first preferred imaging method is ultrasound with doppler. The sensitivity of this method has been reported as 84% (6). Computed tomography (CT) and magnetic resonance imaging (MRI) are often used to rule out other abdominal pathologies, rather than diagnose. Surgical treatment is indicated, and in reproductive-age women, preserving ovarian function is crucial. The assessment of ovarian viability usually involves direct visualization during surgery, but no parameter or marker has reliably indicated existence of necrosis. The assessment of viability often involves direct visualization of a twisted ovary. An enlarged and darkened appearance of the ovary with hemorrhagic lesions is often considered a necrotic sign but can usually be salvaged (7). Despite the common belief among surgeons that the ovary image suggests necrosis, no specific parameter, imaging method, or marker has been proven to reliably indicate necrosis (8).

Delta Neutrophil Index (DNI) is a marker showing the number of immature granulocytes. In a limited number of studies, the DNI was investigated in patient groups with inflammatory processes such as sepsis, acute appendicitis, meningitis, decompensated heart failure, acute gout attack and acute pancreatitis. With this viewpoint, it was thought that it may guide physicians in determining severity of diseases (9). Researchers have recently begun to focus on DNI in diseases characterized by ischemia and necrosis. To our knowledge, this is the first study in the literature to examine the DNI as a sign of ovarian viability in ovarian torsion cases.

The aim of this study is to assess the predictive capability of the preoperative DNI value in deciding whether an oophorectomy is necessary, based on its relation with the final pathology result. If a specific cut-off value can be established, it could provide valuable guidance to surgeons regarding ovarian vitality and the likelihood of necrosis before the planned surgery.

MATERIALS AND METHODS

This retrospective cohort study was conducted in 81 women, aged between 18 and 45 years, who were diagnosed with ovarian torsion in a gynecology department of a tertiary hospital between September 2019 and July 2023. The study was approved by the hospital's Ethical Committee (E2-23-4702). Patients who applied to the emergency department as soon as the pain started, whose complete blood parameters were recorded at the time of admission, and who were diagnosed with ovarian torsion and undergone surgery were included in the study. Patients with any additional diseases which are likely to affect the DNI value (immunological diseases, rheumatological diseases, chronic diseases, or chronic inflammatory diseases, etc.) were excluded from the study. Patients who were pregnant, had to take any kind of medication, were addicted to drugs, or consumed alcohol or tobacco were also excluded. 48 of them had surgical detorsion while 33 of them underwent oophorectomy. Those who had oophorectomy had final pathology results. Patients were first compared as those with detorsion and those with oophorectomy. Then, according to the final pathology results, they were divided into two groups as those with and without necrosis. None of the patients who underwent detorsion required reoperation within the first month. Since there was no material taken in the detorsion group, pathological examination was not performed. The oophorectomy group was reported as congestion and necrosis according to the pathology results. Patients' age, gravida, parity, body mass indexes (BMI), surgery type (detorsion or oophorectomy), how many times the ovary twisted, the time from the first onset of pain to the operation, final histological diagnose and the first onset total blood parameters including the DNI values were reached from hospital records. DNI is calculated using automated hematology analyzers during a complete blood count . It is determined by subtracting the proportion of mature neutrophils from the total granulocyte count. The formula is as follows: DNI = (Total granulocyte count) - (Mature neutrophil count). Both the total granulocyte count and mature neutrophil count are automatically obtained through optical systems and channel-based measurements during CBC analysis(10). In this study, we tried to compare the total blood parameters measured at the time of first admission from the emergency department with the diagnosis of ovarian torsion in both groups (necrosis and congestion) and investigated their usefulness as an auxiliary laboratory indicator in determining the type of surgery to be performed. We aimed to associate the final pathology result and the patients' preoperative admission hemogram parameters especially the DNI values, and evaluated the predictive power of these values in the decision on ovarian-preserving approach.

All statistical analyses were performed using the SPSS for Windows 21.0 (SPSS Inc. IL, USA) software package. A p-value of <0.05 was considered to indicate statistically significant difference. The normality of distribution for variables was assessed using the Shapiro-Wilk test. Data are presented as means ± SD for continuous variables. For all comparisons, the $P<0.05$ value was determined as statistically significant. Independent samples t-test and Mann–Whitney U test were used for comparing groups.

Power analysis was implemented using G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). The difference between two independent mean power analyzes indicated that the study achieved a power of 0.93. This analysis was performed using a comparison of preoperative DNI levels between 21 women with congestion and 12 women with necrosis according to the pathology results.

RESULTS

Table 1 represents the demographic features of women diagnosed with ovarian torsion according to the type of surgery, including age, gravidity, BMI, smoking status, ovarian enlargement, pain onset to surgery and number of ovarian twists. Parameters other than the number of ovarian twists did not statistically significant in deciding the type of operation. It was demonstrated that the kind of procedure changed toward oophorectomy as the number of ovarian twists increased (p<0.05).

Table 2 illustrates the hemogram parameters, ovarian enlargement, time to surgery and number of adnexial twists of the groups according to pathology results. It has been demonstrated that leukocyte count, especially neutrophil count, hematocrit, neutrophil/lymphocyte ratio, delta neutrophil index(%), and number of ovarian twists are statistically significantly higher in patients with necrosis in the pathological examination (p<0.05).

Figure 1 shows a receiver operating characteristic curve which was constructed to select the optimal cut-off values of the DNI and NLR for the identification of necrosis in ovarian torsion cases. For the DNI value, the Area Under the Curve (AUC) was 0.902 with a 95% confidence interval of (0.77 to 1.00; p < 0.001). The optimal cut-off value of 0.70 yielded a specificity of 95.7%, sensitivity of 83.3%, a negative predictive value of 97.1%, and a positive predictive value of 83.3%. For the NLR value, AUC was 0.85 with a 95% confidence interval of (0.76 to 0.941; p < 0.001). The optimal cut-off value of 7.53 resulted in a specificity of 77%, sensitivity of 91.7%, a

Table 1. Demographic features of women diagnosed with ovarian torsion according to the type of surgery

Characteristics	Detorsion Group n=48	Oophorectomy group n=33	p value
Age (year) mean±SD	25.74±5.85	26.2±6.5	0.72
Gravidity mean±SD	0.04±0.2	0.15±0.43	0.15
BMI (kg/m²) mean±SD	23.5±3.37	24.3±3.2	0.24
Smoking +/-	4/43 % (8.5/91.5)	4/30 % (11.8/88.2)	0.71
Over enlargement (mm) mean±SD	73.6±37.1	77.5±32.2	0.62
Pain onset to surgery (hours) mean±SD	38.75±13.92	35.5215.84±0.66	0.63
Twist number (median +IQR)	2(8)	3(6)	**0.044***

*p <0.05 was considered as statistically significant
BMI, body mass index IQR: Inter Quantile Range SD:Standart deviation

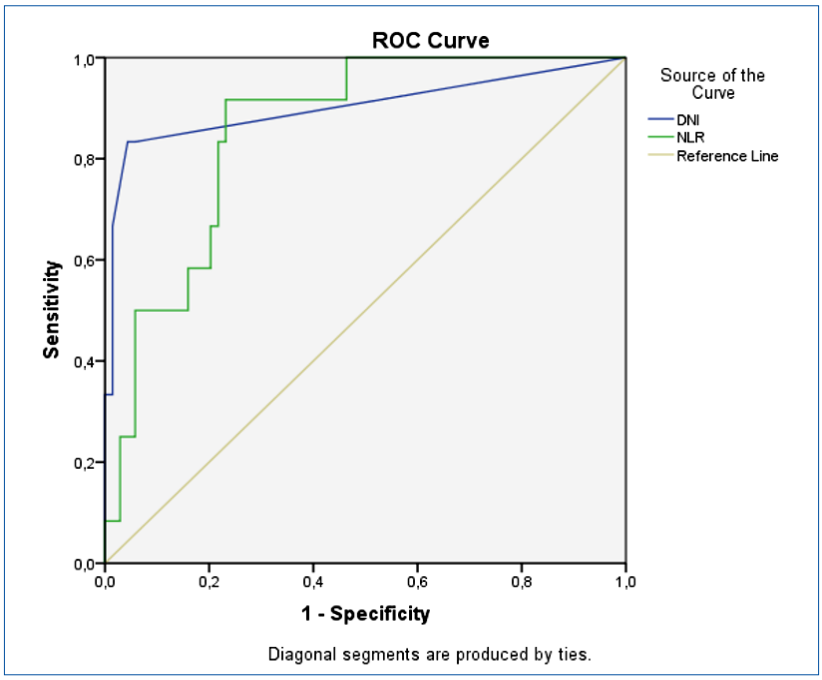

Figure 1. ROC curve for DNI and NLP in torsion cases for the identification of necrosis

Table 2. Hemogram parameters, ovarian enlargement, time to surgery and number of adnexial twists of the groups according to pathology results

Parameters	Congestion group n=21	Necrosis group n=12	p value
Leukocyte count, x10^9 /L	10.4±3.85	14.4±3.96	**0.008***
Neutrophil count, x10^9 /L	8.27±3.73	13.8±3.48	**0.0001***
Lymphocyte count, x10^9 /L	1.53±1.13	1.12±0.59	0.24
Monocyte count, x10^9 /L	0.46±0.28	0.46±0.31	0.99
Hemoglobin, g/dL	12.1±1.57	12.9±1.02	0.09
Hematocrit	36.78±3.9	39.7±2.11	**0.022***
MCV, fL	84.6±8.02	87.3±5.56	0.30
RDW	14.6±2.39	14.4±2.55	0.89
PLT, x10^9 /L	314±72	313±58	0.97
MPV	8.66±0.95	8.40±0.91	0.45
PCT	0.27±0.075	1.01±2.6	0.19
PDW, fL	53.1±8.37	50.1±5.81	0.28
NLR	9.18±9.08	15.5±8.05	**0.048***
DNI(%)	0.3±0.82	3.34±2.98	**0.0001***
PLT/MPV ratio	36.6±8.7	37.8±8.55	0.71
Over enlargment(mm)	81.2±31.8	70.8±34.6	0.38
Pain onset to surgery (hours)	1.48±0.75	1.50±0.52	0.91
Twist number (median +IQR)	3(3)	4(5)	**0.017***

*p <0.05 was considered as statistically significant
MCV, mean corpuscular volume;RDW, red cell distribution width; PLT, platelet count; PCT, plateletcrit; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil/lymphocyte ratio; DNI, delta neutrophil index; IQR: Inter Quantile Range

Table 3. The area under the receiver operating characteristic curve for DNI and NLR

Variables	Cut-off	AUC ± SE	95%CI	Sensitivity %	Specivity %	PPV %	NPV %	p-value
DNI	0.70	0.902±0.65	0.77-1.0	83.3	95.7	83.3	97.1	**<0.001***
NLR	7.53	0.85± 0.047	0.76-0.94	91.7	77	39	98	**<0.001***

*p<0.05 was considered as statistically significant. AUC ± SE,Area Under the Curve±Standart error. 95% CI, Confidence Interval. PPV,Positive Predictive Value. NPV,Negative Predictive Value. NLR, neutrophil/lymphocyte ratio; DNI, delta neutrophil index; NLR, neutrophil to lymphocyte ratio

negative predictive value of 98%, and a positive predictive value of 39%. Receiver operating characteristic(ROC) curve information for NLR and DNI is presented in Table 3.

DISCUSSION

The diagnosis of ovarian torsion is difficult. Generally, the surgeon makes a certain diagnosis by visually during the operation. Although the treatment is surgical, many factors should be considered for the type of surgery. The patient's age, fertility desire, whether she is in reproductive age or not and the appearance of the ovary during surgery are among these factors (11). When the torsion occurs; the first stage is stoppage of blood flow. This is followed by hemorrhage and congestion and ends with necrosis (12,13). There is no method to detect this necrosis before and even during surgery. In this study, we aimed to evaluate the predictive power of preoperative hemogram parameters especially the DNI values in the decision of surgical approach based on its relation with the final pathology result.

Studies so far have tried to find an answer to the question of whether there is a marker that shows necrosis in ovarian torsion before or during surgery. Doppler ultrasound is tradiationally the first choice

imaging method for the diagnosis of torsion. In a prior study, which evaluated ovarian flow and correlated it with histopathologic findings, no association between the ovarian flow on ultrasound and histopathological evidence of necrosis was found (14). Another parameter that can be evaluated with ultrasound is ovarian size. Although studies have argued that ≤5 cm ovarian size may exclude the diagnosis of torsion, the relationship between size and necrosis has not been demonstrated (14,15). In our study, there was no association observed between ovarian enlargement and necrosis.

The relationship between the onset of pain until the surgery starts and necrosis was investigated, but a specific timeframe could not be given. Studies have suggested that the surgery should be performed as early as possible in women who are thought to be torsion, and that it should not be exceeded 24 hours if possible (13,16,17). In our study the onset of pain till the surgery was evaluated and there was no statistically significant difference for choosing the type of surgery between the detorsion or oophorectomy groups (p=0.062). When the histopathological results were evaluated in terms of answering the question of the presence of necrosis or congestion, it was found that onset of pain till the surgery had no statistically significant difference between study groups (p=0.91).

The relation between the number of twist and result in necrosis was also evaluated in our study. There was a statistical significant difference between the congestion and necrosis groups. As the number of rotations increased, the possibility of necrosis also increased (p<0.05).

Although the decision for oophorectomy is made by the surgeon's visual assessment of necrosis during the operation; the previous studies have shown that visual assessment has a low positive predictive value. Novoa et all. stated that only 16% of 33 patients, who were evaluated as visually necrotic and underwent oophorectomy, had histopathologically confirmed necrosis (14). Although there are similar studies, the American College of Obstetricians and Gynecologists (ACOG) recommends against oophorectomy regardless of the appearance of the ovary (18-20).

In a recent study with MRI, one of the advanced imaging modalities, Renganathan et al. conducted a retrospective study on 42 patients to determine whether the ultra-short optimized MRI protocol predicted ovarian necrosis. They concluded that a hypointensity score of 2 or more can diagnose necrosis with high sensitivity and specificity (21). Although the results of this study seem very satisfactory, may not be widely available because the lack of widespread use of MRI and examination costs.

In a study conducted by Mazouni et al., predictive factors for adnexal necrosis in torsion cases were investigated, but no specific predictive factors were identified (8). However, they did emphasize the significance of hyperleukocytosis, with positive and negative predictive values for adnexal necrosis at 21% and 77%, respectively. In our study, we observed similar trends; leukocyte count was significantly higher in the necrosis group (p<0.01).

The DNI is a marker showing the number of immature granulocytes (IGs). IGs are simple to quantify using automatic hematological analyzers and are inflammatory markers that rise after infection and inflammation. Granulocytes with polymorphonuclear neutrophils serve as the initial line of defense for the host against infectious diseases. Within 7–10 days, the progenitor cells in the bone marrow mature into segmented neutrophils. After reaching full maturity, they migrate into the peripheral blood. As a result, sepsis-related enhanced bone marrow activation is indicated by IG formation in the blood. DNI assesses the percentage of IGs in blood circulation. Researchers are investigating the DNI for sepsis severity and inflammatory processes; recently, it has begun to be investigated by some researchers in cases of ischemia and necrosis. Unal et al. found that the DNI effectively aided in the diagnosis of necrotizing pancreatitis. They also argue that the DNI is meaningful in distinguishing between complicated appendicitis and normal appendicitis (22). Another study reported significantly higher DNI levels in the diagnosis of intestinal necrosis due to irreducible hernia (23). According to Cha et al., the DNI was significantly higher during intestinal ischemia caused by strangulation (24). Similarly, Durak et al., mentioned that the DNI can be used to evaluate intestinal necrosis in mesenteric ischemia (25). In light of these findings, we sought to determine if DNI might assist the surgeon in identifying necrosis in ovarian torsion patients before the surgery. In our study, when neutrophil to lymphocyte ratio (NLR) and DNI values were evaluated with histopathological results, both levels were found remarkable higher in patients with histopathologically confirmed necrosis when compared to the patients with congestion and hemorrhage. Notably, when we established a cut-off value of 0.7 (%) for the DNI, the positive predictive value for histopathological necrosis was 83.3%, while the negative predictive value was notably higher at 97.1% (p<0.001). For NLR, using a cut-off value of 7.53, the positive predictive value for histopathological necrosis was 39%, with a highly reliable negative predictive value of 98% below this threshold (p<0.001). These findings suggest that both the DNI and the NLR with the DNI having a greater specificity and negative predictive value and the NLR having a higher sensitivity, are both capable of distinguishing between positive and negative cases for necrosis. Thus, based on our study, having both DNI and NLR values lower than the preoperative total blood count cut-off levels may serve as a guide to surgeons for the absence of necrosis during the surgical evaluation process.

This study has some limitations. It is well established that inflammatory processes have an impact on DNI and NLR. Although those with chronic co-morbidities at the time of administration were excluded from the study, it is unclear whether they had additional acute inflammatory diseases at the time of diagnosis since the study is retrospective.

Additionally, considering this study was conducted with data from a single hospital, the sample size was small. But to minimize potential biases, we investigated every patient with ovarian torsion admitted to our hospital ever since the DNI level became measurable in our hospital.

In conclusion, our study highlights the importance of the DNI, which can easily be calculated using automatic hematological analyzers, as a potential indication for ovarian necrosis in cases of torsion. It also helps the surgeon decide on the operation. While the NLR demonstrates greater sensitivity, the DNI demonstrates higher specificity and a stronger negative predictive value in determining the presence of necrosis. Establishing cut-off values for DNI and NLR can aid in distinguishing necrosis from congestion, prior to proceeding to the surgical process. Surgeons may use readings below the cut-off limits for the preoperative total blood count as helpful guidelines for determining whether necrosis is absent during surgery.

Conflict of interest statement
The authors have no conflicts of interest relevant to this article.

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Analysis of total laparoscopic hysterectomies for benign disease: The experience of a tertiary center: a retrospective cross-sectional study

Benign hastalıklar için yapılan total laparoskopik histerektomilerin analizi: Üçüncü basamak bir merkezin deneyimi: Retrospektif kesitsel çalışma

Fahri Burcin FIRATLIGIL[1], Yıldız AKDAS REIS[2], Arife AKAY[3], Asya KALAYCI ONCU[4], Gulen ERTURUN[5], Ramazan Erda PAY[6], Vakkas KORKMAZ[7], Yaprak ENGIN-USTUN[2]

[1]Department of Perinatology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Obstetrics and Gynecology, Ankara Etlik Zubeyde Hanim Women's Health Education and Research Hospital, Ankara, Türkiye
[3]Department of Obstetrics and Gynecology, Yalova State Hospital, Yalova, Türkiye
[4]Department of Obstetrics and Gynecology, Ercis Sehit Ridvan Cevik State Hospital, Van, Türkiye
[5]Department of Obstetrics and Gynecology, Boyabat 75. Yil State Hospital, Sinop, Türkiye
[6]Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Türkiye
[7]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Türkiye

ABSTRACT

Aim: To present the analysis of pre-, intra- and postoperative outcomes of total laparoscopic hysterectomy (TLH) cases performed in our hospital, a tertiary referral center, over a 5-year period.

Materials and Methods: This retrospective cross-sectional study was conducted in the Gynecology Department of an Education and Research Hospital between January 01, 2017 and December 31, 2021. Clinical data and laboratory results were obtained from medical and hospital records. After analyzing these patients, the patients were divided into two groups based on their body mass index and the pre-, intra- and postoperative results were also compared.

Results: The mean age of 516 patients included in the study was 47.4 ± 8.94 years. The most common indication for hysterectomy was endometrial premalignant lesions (23.9%). The overall intra-operative complication rate was 0.78%. The most common intra-operative complication in the overall population was bladder damage.Postoperative complications: 7 wound infections (1 vs. 6); 5 vaginal bleedings (0 vs. 5); 3 abscesses in the vaginal cuff (1 vs. 2); 2 septic shock (0 vs. 2); 2 disorders of the general condition (0 vs. 2); 1 urinary tract infection (1 vs. 0); 1 umbilical hernia (1 vs. 0) and positional nerve damage (0 vs. 1), respectively for the groups.

Conclusion: TLH is now a minimally invasive surgical procedure which can be performed safely and with very few complications as surgical experience and technical equipment improves. A higher complication rate has been reported in earlier cases, but both in the present study and in more recent studies, a very low complication rate was found with the procedure. Therefore, as recommended by the ACOG, this procedure can be used as the preferred method for patients in whom hysterectomy is planned primarily for benign conditions.

Keywords: Hysterectomy; laparoscopy; surgeon experience; uterine fibroid

ÖZ

Amaç: Üçüncü basamak bir sevk merkezi olan hastanemizde 5 yıl boyunca gerçekleştirilen total laparoskopik histerektomi (TLH) olgularının ameliyat öncesi, sırası ve sonrası sonuçlarının analizini sunmaktır.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışma, 01 Ocak 2017 ile 31 Aralık 2021 tarihleri arasında bir Eğitim ve Araştırma Hastanesi Kadın Hastalıkları Kliniğinde gerçekleştirilmiştir. Klinik veriler ve laboratuvar sonuçları tıbbi kayıtlardan ve hastane kayıtlarından elde edilmiştir. Bu hastalar analiz edildikten sonra, hastalar vücut kitle indekslerine göre iki gruba ayrılmış ve ameliyat öncesi, sırası ve sonrası sonuçlar da karşılaştırılmıştır.

Bulgular: Çalışmaya dahil edilen 516 hastanın yaş ortalaması 47,4 ± 8,94 idi. Histerektomi için en yaygın endikasyon endometriyal premalign lezyonlardı (%23,9). Genel intra-operatif komplikasyon oranı %0,78 idi. Genel popülasyonda en sık görülen intra-operatif komplikasyon mesane hasarıydı. Ameliyat sonrası komplikasyonlar: Gruplar için sırasıyla 7 yara enfeksiyonu (1'e karşı 6); 5 vajinal kanama (0'a karşı 5); vajinal kafta 3 apse (1'e karşı 2); 2 septik şok (0'a karşı 2); 2 genel durum bozukluğu (0'a karşı 2); 1 idrar yolu enfeksiyonu (1'e karşı 0); 1 umbilikal herni (1'e karşı 0) ve pozisyonel sinir hasarı (0'a karşı 1).

Sonuç: TLH, cerrahi deneyim ve teknik donanım geliştikçe artık güvenli bir şekilde ve çok az komplikasyonla uygulanabilen minimal invaziv bir cerrahi prosedürdür. Daha önceki vakalarda daha yüksek bir komplikasyon oranı bildirilmiştir, ancak hem bu çalışmada hem de daha yeni çalışmalarda prosedürle ilgili çok düşük bir komplikasyon oranı bulunmuştur. Bu nedenle, ACOG tarafından önerildiği gibi, bu prosedür öncelikle iyi huylu durumlar için histerektomi planlanan hastalarda tercih edilen yöntem olarak kullanılabilir.

Anahtar Kelimeler: Histerektomi; laparoskopi; cerrah deneyimi; uterin myom

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Sorumlu Yazar/Corresponding Author: Fahri Burcin FİRATLİGİL, Department of Obstetrics and Gynecology, Ankara Bilkent City Hospital, Ankara, Türkiye
E-mail: md.fahri@gmail.com

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INTRODUCTION

Nowadays, hysterectomy is one of the most common gynecological operations. The number of hysterectomies in the USA is estimated to be about 60,000 per year (1), while in India about 2,310,263 women undergo hysterectomy annually (2). More than 70% of hysterectomies are performed for benign causes such as menorrhagia (abnormal uterine bleeding), uterine fibroids, pelvic pain and uterine prolapse (3). Although these procedures have traditionally been performed abdominally (TAH) and vaginally (VH), minimally invasive techniques are increasingly being used due to innovations of medical technology (4). These techniques include laparoscopically assisted vaginal hysterectomy (LAVH), total laparoscopic hysterectomy (TLH) and robot-assisted laparoscopic hysterectomy.

Reich et al. reported on the first TLH in 1989 (5). Since then, there have been a number of improvements in the field of laparoscopic-assisted hysterectomies. In TLH, all surgical incisions, dissections and suturations (including closure of the vaginal cuff) are performed entirely through the trocars. Compared to other conventional methods, it is characterized by shorter operating times, less blood loss and shorter hospital stays (6). Despite all these advantages, however, TAH is still the most commonly used form of hysterectomy. This is mainly due to the lack of experience of the doctors and support staff, the lack of technical equipment and a higher incidence of complications such as injuries to the ureter, bladder and bowel near the genital organs as well as injuries to the great vessels when inserting the trocars (7).

In this context, we aimed to present the analysis of pre-, intra- and postoperative outcomes of TLH cases performed in our hospital, a tertiary referral center, over a 5-year period.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted in the Gynecology Department of an Education and Research Hospital between January 01, 2017 and December 31, 2021. The study was approved by the local ethics committee for scientific research (May 26, 2022; No. 2022/06) and was conducted in accordance with the principles of the Declaration of Helsinki. In view of the retrospective nature of the study, the ethics committee waived the required patient consent. All patient data was anonymized or treated confidentially.

Inclusion and exclusion criteria

Patients who had undergone TLH surgery with benign and premalignant disease were included in the study.

Patients were excluded from the study if any of the following applied to them: missing data, TLH surgery for malignancy, uterine fibroids ≥ 10 cm and pregnancy-related circumstances.

Data

The study included 516 patients who had undergone TLH. Data from 516 patients were obtained from patient files and hospital records. Data included age, body mass index (BMI), gravidity, parity, previous cesarean section, previous surgery or gynecologic procedures, TLH indications, laboratory test results [pre- and postoperative white blood cell (WBC) count and hemoglobin (HB)], Delta hemoglobin (ΔHB) (the ΔHB is calculated using the formula [preoperative HB] - [postoperative HB]), hospitalization days, blood transfusions and chronic diseases, etc.

Evaluation of the patients

Patients with benign or premalignant disease for whom hysterectomy is indicated are treated according to the corresponding TLH protocol.

Abdominal and transvaginal ultrasound examinations of the patients were performed prior to surgery using a General Electric Voluson 730® (1.5-4.5 MHz probe, Waukesha, WI, USA). Laboratory analyzes [complete blood count (CBC)] of patients who had undergone TLH are analyzed using the Advia® 120 hematology system (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois).

Details of TLH surgery

A supraumbilical port with a diameter of ten millimeters was used as the primary trocar. Three lateral trocars were used. A bipolar electrocautery or a LigaSure laparoscopic sealer (5 and 10 mm) was used to coagulate the pedicles and scissors were used for cutting. Colpotomy was performed with a monopolar electrocautery hook. Salpingo-oophorectomy was performed if the patient was postmenopausal or had significant ovarian pathology, otherwise the ovaries were preserved. The vaginal cuff was usually closed laparoscopically using the intracorporeal knotting technique. In all cases, the bilateral ureters were traced from the pelvic edge to the bladder entrance, especially in previously operated cases in which the course of the ureter was disturbed due to adhesions. In some cases, the adhesions were removed by sharp and blunt dissections using bipolar electrocautery and scissors.

Study design

A total of 516 patients who met the inclusion criteria mentioned in the Material and Methods section and underwent TLH surgery were included in the study. After analyzing these patients, the patients were divided into two groups: those with a BMI < 30 kg/m^2 (Group I) and those with a BMI ≥ 30 kg/m^2 (Group II), and the pre-, intra- and postoperative outcomes were also compared.

Statistical analyses

Data analysis was performed using IBM's Social Sciences Statistical Package Version 29.0 (SPSS ver 29.0). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check whether the numerical data correspond to a normal distribution. Numerical data are expressed as mean ± standard deviation. Categorical variables were expressed as numbers (percentages) and analyzed using the chi-square test, with odds ratios (OR) expressed with 95% confidence intervals. In this study, which consisted of two independent groups, the t-test for independent samples was also used for parametric variables. Statistical significance was accepted as a p value <0.05.

RESULTS

After reviewing patient files and hospital records, 564 patients were found who had undergone TLH surgery. After applying exclusion criteria, 516 patients were included in the study. The 516 patients were divided into two groups: those with a BMI < 30 kg/m^2 (Group I) (n=260) and those with a BMI ≥ 30 kg/m^2 (Group II) (n=256). The flow chart of the participants is shown in Figure 1.

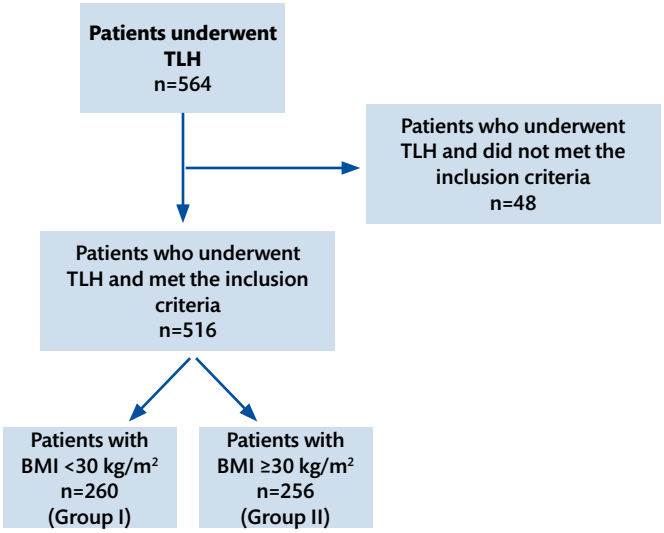

Figure 1. The flow chart of the participants

The demographic, pre- and post-operative laboratory analysis of the patients is shown in Table 1. The mean age of the 516 patients was 47.4 ± 8.94 years. Group II had a statistically significantly higher average age than Group I. Although there was no statistically significant difference in the pre-operative WBC and HB values between the groups, the post-operative HB was statistically

Table 1. The demographic, pre- and post-operative laboratory analysis of the patients

		Total patients n=516	Groups		p
			Group I n=260	Group II n=256	
Age (years) (mean ± SD)		47.4 ± 8.94	46.0 ± 10.56	48.9 ± 6.63	**<0.001** [a]
Gravidity (mean ± SD)		2.9 ± 1.76	2.5 ± 1.67	3.3 ± 1.77	**<0.001** [a]
Parity (mean ± SD)		2.3 ±1.34	2.0 ± 1.32	2.5 ± 1.32	**<0.001** [a]
Previous CS n (%)	No	442 (85.7)	224 (86.2)	218 (85.2)	0.746 [b]
	Yes	74 (14.3)	36 (13.8)	38 (14.8)	
BMI (kg/m²) (mean ± SD)		29.7 ± 11.05	24.8 ± 2.50	34.6 ± 13.86	**<0.001** [a]
Preoperative WBC (cells/mm³) (mean ± SD)		7.050 ± 1.916	7.048 ± 1.967	7.052 ± 1.867	0.492 [a]
Preoperative HB (g/dL) (mean ± SD)		11.3 ± 3.63	11.3 ± 3.99	11.3 ± 3.23	0.404 [a]
Postoperative WBC (cells/mm³) (mean ± SD)		10.665 ± 3.417	10.899 ± 3.467	10.428 ± 3.357	0.059 [a]
Postoperative HB (g/dL) (mean ± SD)		9.4 ± 3.22	9.7 ± 3.29	9.0 ± 3.13	**0.012** [a]
Delta HB (g/dL) (mean ± SD)		1.93 ± 4.44	1.57 ± 4.69	2.29 ± 4.15	**0.033** [a]
Blood transfusion (mean ± SD)		0.09 ± 0.44	0.08 ± 0.413	0.10 ± 0.474	0.333 [a]
Transfusion n (%)	None	490 (95)	249 (95.8)	241 (94.1)	0.554 [b]
	Postoperative ES	13 (2.5)	4 (1.5)	9 (3.5)	
	Preoperative ES	8 (1.6)	4 (1.5)	4 (1.6)	
	Postoperative Ferric Carboxymaltose	4 (0.8)	2 (0.8)	2 (0.8)	
	Intraoperative ES	1 (0.1)	1 (0.4)	0 (0)	
	Total Transfusion	26 (5)	11 (4.2)	15 (5.9)	
Hospital stay (days) (mean ± SD)		2.23 ± 1.41	2.09 ± 1.12	2.37 ± 1.65	**0.013** [a]

Abbreviations: CS: cesarean section; ES: erythrocyte suspension; HB: hemoglobin; SD: standart deviation; WBC: white blood cell
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.
[a] Student t test [b] Chi Square test

significantly lower in Group II than in Group I (p=0.012). ΔHB values were statically significant higher in Group II than Group I (p=0.033). There was no statistical difference between the groups in terms of the number of transfusions (p=0.333). The duration of hospitalization was statistically significantly higher in Group II (p=0.013).

The analysis of chronic diseases and the patients' history of previous surgical interventions (gynecologic or non-gynecologic) is shown in Table 2. While there was no difference between the groups in terms of previous gynecologic surgery, there was a statistically significant difference in terms of previous non-gynecologic surgery (p<0.001). While appendectomy and cholecystectomy surgeries were more common in Group II, mastectomy surgeries were significantly more common in Group I. Among chronic diseases, cases of hypertension were higher in Group II (p<0.001).

A comparison of the indications for TLH, intra- and post-operative complications, concomitant other surgical procedures, etc. is shown in Table 3. The groups showed significant differences in terms of the indications for TLH (p<0.001). Statistically significant TLH indications for Group I are uterine fibroids and gender affirmation surgery. Statistically significant TLH indications for Group II are persistent bleeding and premalignant endometrial lesions. In Group II, ureteral damage was diagnosed in 1 case and bladder damage in 2 cases, while in Group I, bladder damage was diagnosed in only 1 case. Postoperative complications were statistically significantly higher in Group II (p=0.002). Postoperative complications: 7 wound infections (1 vs. 6); 5 vaginal bleedings (0 vs. 5); 3 abscesses in the vaginal cuff (1 vs. 2); 2 septic shock (0 vs. 2); 2 disorders of the general condition (0 vs. 2); 1 urinary tract infection (1 vs. 0); 1 umbilical hernia (1 vs. 0) and positional nerve damage (0 vs. 1), respectively. None of our patients developed intra- or postoperative deep vein thrombosis, thrombotic events or pulmonary thromboembolism. The OR for postoperative complications for Group II was 4.84 (95% CI 1.615-14.508).

In three Group II cases, laparoscopy was replaced by laparotomy in the intra-operative phase (cervical premalignant lesion, adnexal mass and endometrial premalignant lesion).

Table 2. The analysis of chronic diseases and the patients' history of previous surgical interventions

		Total patients n=516	Groups		p
			Group I n=260	Group II n=256	
Previous gynecologic surgery n (%)	None	471 (91.3)	239 (91.9)	232 (89.6)	0.366*
	Endometriosis	1 (0.2)	1 (0.4)	0 (0)	
	Myomectomy	6 (1.2)	4 (1.4)	2 (0.8)	
	Other gynecologic surgeries	25 (4.8)	10 (3.9)	15 (5.8)	
	BTL	11 (2.1)	4 (1.6)	7 (2.7)	
	Prolapsus	2 (0.8)	2 (0.8)	0 (0)	
Previous non- gynecologic surgery n (%)	None	385 (74.6)	198 (76.2)	187 (73)	**<0.001***
	Appendectomy	32 (6.2)	7 (2.7)	25 (9.8)	
	Cholecystectomy	19 (3.7)	5 (1.4)	14 (5.5)	
	Thyroidectomy	9 (1.7)	3 (1.2)	6 (2.3)	
	Mastectomy	39 (7.6)	27 (10.4)	12 (4.7)	
	Other surgeries	32 (6.2)	20 (7.7)	12 (4.7)	
HT n (%)	No	442 (85.7)	238 (79.7)	204 (79.7)	**<0.001***
	Yes	74 (14.3)	22 (8.5)	52 (20.3)	
DM n (%)	No	468 (90.7)	242 (93.1)	226 (88.3)	0.061*
	Yes	48 (9.3)	18 (6.9)	30 (11.7)	
Lung diseases n (%)	No	502 (97.3)	256 (98.5)	246 (96.1)	0.098*
	Yes	14 (2.7)	4 (1.5)	10 (3.9)	
Other chronic diseases n (%)	Cardiovascular	7 (1.4)	5 (1.9)	2 (0.8)	0.102*
	Mammary CA	18 (3.5)	10 (3.8)	8 (3.1)	
	Thyroid diseases	26 (5)	18 (6.9)	8 (3.1)	

Abbreviations: BTL: bilateral tubal ligation; CA: cancer; DM: diabetes mellitus; HT: hypertension
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.
*Chi Square test

Table 3. A comparison of the indications for TLH, intra- and post-operative complications, concomitant other surgical procedures

		Total patients n=516	Groups		p
			Group I n=260	Group II n=256	
TLH indications n (%)	Uterine fibroids	87 (16.9)	63 (24.2)	24 (9.4)	**<0.001***
	Persistant uterine bleeding	111 (21.6)	48 (18.5)	63 (24.6)	
	EPL	123 (23.9)	42 (16.2)	81 (31.8)	
	Adenomyosis	20 (3.9)	10 (3.8)	10 (3.9)	
	BRCA (+) prophylaxis	20 (3.9)	14 (5.4)	6 (2.4)	
	Adnexal mass	46 (8.9)	23 (8.8)	23 (8.8)	
	CPL	39 (7.5)	13 (5)	26 (10.2)	
	PMB	34 (6.5)	14 (5.4)	20 (7.8)	
	Gender affirmation surgery	36 (6.9)	33 (12.7)	3 (1.1)	
BS/BSO/USO surgery with TLH n (%)	BS	133 (25.8)	72 (27.7)	61 (23.8)	0.355*
	BSO	342 (66.3)	171 (65.8)	171(66.8)	
	USO	41 (7.9)	17 (6.5)	24 (9.4)	
Additional surgical intervention n (%)	No	478 (92.6)	245 (94.2)	233 (91)	0.425*
	Bladder repair	3 (0.6)	1 (0.4)	2 (0.8)	
	Adhesiolysis	21 (4)	9 (3.4)	12 (4.6)	
	Ureteroneocystostomy	1 (0.2)	0(0)	1 (0.4)	
	Perineoplasty / Vaginoplasty	5 (1)	1 (0.4)	4 (1.6)	
	TOT	5 (1)	3 (1.2)	2 (0.8)	
	Cholecystectomy	2 (0.4)	0(0)	2 (0.8)	
	Appendectomy	1 (0.2)	1(0.4)	0 (0)	
Intraoperative Complications n (%)	No	512 (99.2)	259 (99.6)	253 (98.8)	0.308*
	Yes	4 (0.8)	1 (0.4)	3 (1.2)	
Postoperative Complications n (%)	No	494 (95.7)	256 (98.5)	238 (93)	**0.002***
	Yes	22 (4.3)	4 (1.5)	18 (7)	

Abbreviations: BRCA:BReast CAncer gene; BS: bilateral salpingectomy; BSO: bilateral salpingo-oophorectomy; CPL: cervical premalignant lesion; EPL: endometrial premalignant lesion; PMB: postmenopausal bleeding; TLH: total laparoscopic hysterectomy; TOT: transobturator tape; USO: unilateral salpingo–oophorectomy.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.
*Chi Square test

The vaginal cuff was closed vaginally in 2 Group II cases. All other TLH cases were closed using the laparoscopic intra-corporeal suture technique.

DISCUSSION

In recent years, laparoscopic surgery has become one of the most frequently used surgical methods in gynecological practice. This surgical method has also become established for hysterectomy, one of the most common surgical procedures in gynecological departments. In the committee statement published by the American College of Obstetricians and Gynecologists (ACOG) in 2017, it was mentioned that VH and LH, which are minimally invasive methods, should be preferred as much as possible in surgical experience and patient selection, and even TLH should be the standard method in patients for whom VH are not suitable (8). With this in mind, we provide an overview of the analysis of TLHs performed for benign conditions at our tertiary referral hospital where minimally invasive surgery is used effectively.

In the retrospective 5-year period, 564 patients underwent TLH and 516 patients met the inclusion criteria and were included in our study. If we look at the total number of cases in 5 years, we see that 564 TLH cases is a good number. In the Cheung et al. study (9), the number of cases in 5 years was 175, but when we look at the time frame of the study, we realize that it was conducted about 10 years before our study. This low number is probably due to lack of surgical experience and technical inadequacies. In our study, the mean age is 47.4 ± 8.94 years, and also the mean age is 46.0 ± 10.56 years in Group I and 48.9 ± 6.63 years in Group II, respectively. A study by Ashfaq et al. (10) examined the experience

of a single surgeon on the results of TLH procedures and found an average age of 46.42 ± 5.01 years. In a retrospective analysis of 361 TLH cases by Mereu et al. (11), they arrived at a mean age of 49.6 ± 6.5 years.

In our study, the indications for TLH were endometrial premalignant lesions, treatment-resistant uterine bleeding and uterine fibroids. Uterine fibroids were the most common indication in the group with a BMI <30 kg/m^2, while endometrial premalignant lesions and treatment-resistant uterine bleeding were more common in Group II with a BMI ≥30 kg/m^2. In the literature, uterine fibroids are mentioned as the most common indication, followed by abnormal uterine bleeding and endometriosis (8,10). Another study by Antoun et al (12) concluded that the most common reasons for TLH in the 128 patients were pelvic pain (45%), followed by uterine fibroids (21%) and abnormal uterine bleeding (18%). The results of our study are partly compatible with these indications.

The present study included 74 (14.3%) patients had a history of cesarean section, with no differences between groups (n=36 vs. n=38); when we examined rates of previous laparotomies, 202 patients had a history of abdominal surgery (including gynecologic, non-gynecologic, and cesarean section). There was no difference between the groups in terms of previous abdominal surgery. Previous abdominal surgery is not a contraindication for laparoscopic surgery, but the risk of bladder and bowel injury is sometimes increased in these patients (13). We have four intra-operative complications: in Group II, ureteral damage was diagnosed in 1 case and bladder damage in 2 cases, while in Group I, bladder damage was diagnosed in only 1 case. However, there were no significant differences between the groups with regard to intra-operative complications. Postoperative complications were higher in Group II with a BMI ≥ 30 kg/m^2. In the literature, there are conflicting results in studies on BMI-related TLH complications (14-16). Jayashree et al (14) concluded that there were no differences in intra- and postoperative parameters between overweight women compared to women with a normal BMI. Another study by Otake et al (15) found that overweight patients had longer operation times and more postoperative complications than normal-weight patients. In an Egyptian study, the authors concluded that TLH can be successfully performed in obese patients, although a BMI between 30-39.9 kg/m^2 has higher peri-operative clinical and financial consequences compared to non-obese patients (BMI<30 kg/m^2) (16).

There was no statistical difference between the preoperative HB values of the groups, the postoperative HB value of Group II was statistically lower and the ΔHB value, which indicates the intra-operative HB change, was statistically significantly higher than Group I. Thus, overweight patients have a higher risk of blood loss in TLH cases. In contrast to our study, Andan et al. reported that BMI has no effect on the amount of bleeding in TLH (17). A study by Nawfal et al. also found that BMI did not increase the amount of intra-operative bleeding (18). In agreement with our study, Heinberg et al. (19) reported that the risk of intra-operative blood loss was increased in obese women compared to non-obese women and that this risk tripled with blood loss of more than 500 ml.

In conclusion, due to improved surgical experience and technical equipment, TLH is now a minimally invasive surgical procedure that can be performed safely and with very few complications. In earlier cases, a higher complication rate was reported, but both in this study and in more recent studies, a very low complication rate was found for the procedure. Therefore, as recommended by the ACOG, this procedure can be used as the method of choice for patients who are primarily scheduled for hysterectomy for benign conditions. However, particular attention should be paid to complications and blood loss in overweight women.

The strengths and limitations

The study was conducted in a tertiary referral hospital and standardized protocols and surgical methods were used for all patients. The treatment and care of all patients in the study was coordinated in the gynecology department, which had a sufficient number of concomitant cases.

However, due to the retrospective design of the study, data/information was missing for some patients (duration of laparoscopic surgery, uterine weight, etc.). As the study was planned in a single center, we also lacked experience with different surgical techniques and approaches.

Competing interests

The authors declare that they have no competing interests.

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There is no financial disclosure to be made for this study.

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Authors' contributions

Conceptualization, F.B.F and Y.A.R; methodology, F.B.F, Y.A.R. and A.A.; software, A.A., A.K.O. and G.E.; validation, A.A. and G.E.; formal analysis, A.A., A.K.O. and G.E.; investigation, F.B.F., Y.A.R., R.E.P., and V.K.; resources, A.K.O, G.E., and R.E.P.; data curation, G.E. and R.E.P.; writing—original draft preparation, F.B.F.; writing—review and editing, F.B.F. and Y.E-U.; visualization, V.K. and Y.E-U.; supervision, Y.E-U; project administration, F.B.F., Y.A.R., V.K. and Y.E-U.

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The impact of polycystic ovary syndrome on tubal ectopic pregnancy risk during first pregnancy

Polikistik over sendromunun ilk gebelikte tubal ektopik gebelik riski üzerindeki etkisi

Busra KORPE[1], Samet Kutluay ERGORUN[1,2], Sumeyye MERMI[1], Caner KOSE[1]

[1]Ankara Etlik City Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye
[2]Duzce Atatürk State Hospital, Department of Gynecology and Obstetrics, Duzce, Türkiye

ABSTRACT

Aim: This study aimed to investigate the effect of Polycystic Ovary Syndrome (PCOS) on the risk of tubal ectopic pregnancy during first pregnancy and how this risk varies across different PCOS phenotypes.

Materials and Methods: This retrospective study analyzed 657 women diagnosed with ectopic pregnancy between November 2022 and November 2024 at a tertiary care hospital. Of these, 222 women had confirmed tubal ectopic pregnancies and a documented diagnosis of PCOS at the same center. The participants were divided into two groups based on the Rotterdam criteria: PCOS (n=76) and non-PCOS (n=146). PCOS phenotypes were further classified as Phenotype A (hyperandrogenism, oligo-/anovulation, and PCOM), Phenotype B (hyperandrogenism and oligo-/anovulation), Phenotype C (hyperandrogenism and PCOM), and Phenotype D (oligo-/anovulation and PCOM).

Results: Women with PCOS had a significantly higher incidence of tubal ectopic pregnancy during their first pregnancy compared to non-PCOS women (OR: 4.42, 95% CI: 2.22–8.80, $p < 0.001$). Among PCOS phenotypes, Phenotype C (hyperandrogenism and polycystic ovarian morphology) was the most common (32.9%), followed by Phenotype D (23.7%). Non-PCOS women exhibited higher rates of conventional risk factors, such as intrauterine device use, pelvic inflammatory disease (PID), and previous pelvic surgeries.

Conclusion: PCOS may be associated with an increased risk of tubal ectopic pregnancy, especially during the first pregnancy. The findings suggest that hormonal and structural disruptions in PCOS, may impair fallopian tube function and embryo transport. These results underscore the need for targeted fertility counseling and management strategies in women with PCOS to mitigate ectopic pregnancy risks.

Keywords: Ciliary motility disorders, ectopic pregnancy, fallopian tubes, polycystic ovary syndrome

ÖZ

Amaç: Bu çalışmanın amacı, Polikistik Over Sendromunun (PKOS) ilk gebelikte tubal ektopik gebelik riskine olan etkisini ve bu riskin farklı PKOS fenotiplerine göre nasıl değiştiğini incelemektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Kasım 2022- Kasım 2024 tarihleri arasında üçüncü basamak bir hastanede ektopik gebelik tanısı alan toplam 657 kadın incelendi. Bu kadınlardan 222'sinde hem doğrulanmış tubal ektopik gebelik hem de aynı merkezde tanı almış PKOS tanısı bulunuyordu. Hastalar, Rotterdam kriterlerine göre iki gruba ayrıldı: PKOS'lu (n=76) ve PKOS olmayan (n=146). PKOS'lu kadınlar ayrıca şu fenotiplere göre sınıflandırıldı. PKOS fenotipleri, Fenotip A (hiperandrojenizm, oligo-/anovulasyon, polikistik over morfolojisi [PKOM]), Fenotip B (hiperandrojenizm, oligo-/anovulasyon), Fenotip C (hiperandrojenizm, PKOM) ve Fenotip D (oligo-/anovulasyon, PKOM) olarak sınıflandırıldı.

Bulgular: PKOS'lu kadınlarda ilk gebeliklerinde, PKOS olmayan kadınlara kıyasla anlamlı derecede daha yüksek tubal ektopik gebelik insidansı gözlendi (OR: 4.42, 95% CI: 2.22–8.80, $p < 0.001$). PCOS fenotipleri arasında Fenotip C (hiperandrojenizm ve PKOM) en yaygın olanıydı (%32.9), ardından Fenotip D (%23.7) geldi. PKOS olmayan kadınlar, daha yüksek oranlarda geleneksel risk faktörleri (rahim içi araç, pelvik inflammatuar hastalık, önceki pelvik cerrahiler) gösterdi.

Sonuç: PKOS, özellikle ilk gebelik sırasında tubal ektopik gebelik riskini artırabilir. Hormonal ve yapısal bozukluklar, fallop tüpü fonksiyonlarını ve embriyo taşınmasını bozarak bu riski artırabilir. Bulgular, PKOS'lu kadınlarda ektopik gebelik riskini azaltmaya yönelik hedefe yönelik fertilite danışmanlığı ve yönetim stratejilerinin önemini vurgulamaktadır.

Anahtar kelimeler: Ektopik gebelik, fallop tüpleri, polikistik over sendromu, silyer motilite bozuklukları,tubal geçirgenlik

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Sorumlu Yazar/Corresponding Author: Busra KORPE, Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Türkiye
E-mail: busraejderoglu@yahoo.com

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that affects women of reproductive age, presenting with symptoms such as hyperandrogenism, menstrual irregularities, and polycystic ovarian morphology (PCOM) (1). PCOS is often associated with ovulatory dysfunction, insulin resistance, and chronic low-grade inflammation, all of which can have systemic effects beyond ovarian function alone (2,3). While much of the research on PCOS has focused on its impact on ovulation and fertility, there is growing interest in its potential effects on the fallopian tubes, particularly in the context of tubal patency and ciliary function (2-7).

Tubal patency, the openness and functional capacity of the fallopian tubes, is crucial for normal fertility, as it allows for the transport of sperm, eggs, and embryos through the reproductive tract (8,9). In women with PCOS, however, hormonal imbalances and inflammatory processes may impair tubal patency, increasing the risk of abnormal embryo implantation outside the uterine cavity (2,3,10). Additionally, the ciliated cells lining the fallopian tubes play an essential role in the directed movement of the embryo toward the uterus (11). Studies suggest that the hyperandrogenism and altered hormonal milieu characteristic of PCOS may reduce ciliary activity, potentially disrupting this delicate transport process (12-14).

The combined effects of altered tubal patency and reduced ciliary activity may contribute to a higher incidence of tubal ectopic pregnancies among women with PCOS (15,16). The primary objective of this study was to investigate how PCOS, particularly hormonal and structural disruptions associated with this condition, influences the risk of tubal ectopic pregnancy during the first pregnancy. We further aimed to analyze variations in risk according to different PCOS phenotypes.

MATERIALS AND METHODS

This retrospective cohort study included 657 women diagnosed with ectopic pregnancy at a tertiary hospital between November 2022 and November 2024. Approval for the study protocol was obtained from the Institutional Review Board. Participants provided informed consent during hospital admission, permitting their medical records to be utilized for future research purposes. The study strictly followed the ethical guidelines outlined in the Declaration of Helsinki.

Women with non-tubal ectopic pregnancies (e.g., cervical, interstitial, ovarian, or abdominal), incomplete medical records, or missing data regarding PCOS or ectopic pregnancy characteristics were excluded. Additional exclusions included women diagnosed with infertility who underwent assisted reproductive technology (ART) or ovulation induction treatments, those with a history of uterine or ovarian malignancy, congenital uterine anomalies (e.g., bicornuate uterus), systemic illnesses affecting reproductive outcomes (e.g., uncontrolled diabetes, severe thyroid dysfunction, or systemic lupus erythematosus), and those who declined or were unable to provide informed consent. Figure 1 shows the flow chart of the study.

A total of 222 women with confirmed tubal ectopic pregnancies were included in the study. Diagnosis was made based on a combination of clinical presentation, ultrasound findings, and laboratory markers. Ultrasound findings supporting the diagnosis included the absence of an intrauterine pregnancy along with the presence of an adnexal mass or free fluid in the pelvis. Additionally, periodic measurements of human chorionic gonadotropin (HCG) levels further confirmed the diagnosis (17,18). These criteria ensured accurate and reliable identification of tubal ectopic pregnancies within the study population.

To assess the presence of polycystic ovary syndrome (PCOS), each participant's medical history was reviewed, and previous diagnoses of PCOS at the same hospital were confirmed through medical records. The Rotterdam criteria were consistently applied to define PCOS within the cohort (19). According to these criteria, the diagnosis of PCOS requires at least two of the following: PCOM on ultrasound, clinical or biochemical signs of hyperandrogenism or hirsutism, and evidence of anovulation. Women with a confirmed diagnosis of PCOS were grouped accordingly, while those without a prior PCOS diagnosis (n=76) were placed in the non-PCOS group (n=146) (Figure 1).

PCOS phenotypes were categorized as follows: Phenotype A included clinical or biochemical hyperandrogenism, oligo-/anovulation, and PCOM; Phenotype B consisted of hyperandrogenism along with oligo-/anovulation; Phenotype C involved hyperandrogenism and PCOM; and Phenotype D was characterized by oligo-/anovulation combined with PCOM (20).

Data were collected at the time of admission and supplemented with information from electronic medical records. The variables included demographic characteristics (age, BMI, smoking status), reproductive history (parity, previous ectopic pregnancies), history of pelvic inflammatory disease (PID), history of tubal and pelvic surgeries, presence of intrauterine device (IUD) and duration of infertility if infertility treatments were present), and clinical parameters related to PCOS, such as a history of anovulation and PCOM findings.

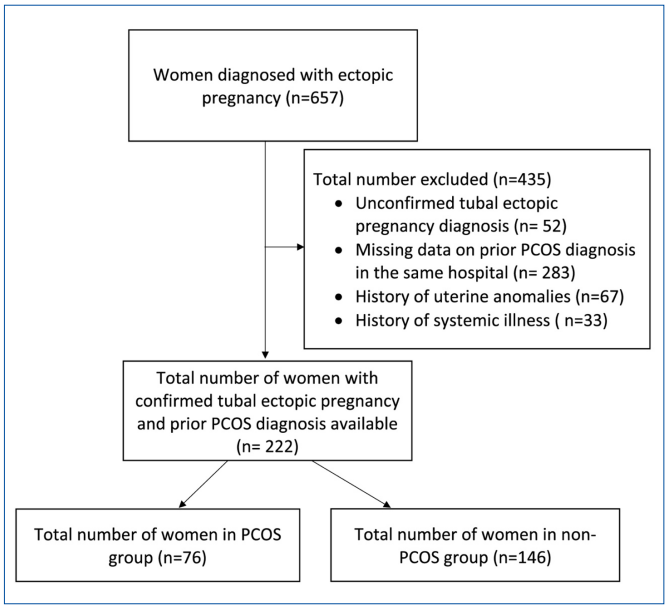


Figure 1. Flow chart of the study

Statistical Analysis

Statistical analyses were performed using SPSS software (version 26). The normality of continuous variables was assessed visually using histogram plots and by evaluating skewness and kurtosis values. Continuous variables were compared between the PCOS and non-PCOS groups using independent t-tests. Categorical variables were analyzed with Chi-square or Fisher's exact tests, depending on the distribution of the data. To examine the association between PCOS and tubal ectopic pregnancy, logistic regression analysis was conducted, adjusting for potential confounders such as age, BMI, history of PID, and history of tubal or pelvic surgeries. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to quantify the strength of the association between PCOS and the risk of ectopic pregnancy. A p-value of < 0.05 was considered statistically significant.

Table 1. Demographic and Clinical Characteristics of Study Participants

	(N =222)
Age (y) (mean±SD)	30.37±4.57
BMI (kg/m²) (mean±SD)	25.37±4.35
Infertility time (month) (median,min-max)	6.36±13.65
Gravidity (median,min-max)	3 (1-7)
Parity (median,min-max)	1 (0-4)
Abortus (median,min-max)	1 (0-3)
	N (%)
History of Ectopic pregnancy	
no	121 (54.5)
1 time	91 (41)
2 times	10 (4.5)
History of Ectopic Pregnancy in the First Pregnancy	
No	177 (79.7)
Yes	45 (20.3)
Smoking	
No	143 (64.4)
Yes	79 (35.6)
Presence of Intrauterine Device	
No	196 (88.3)
Yes	26 (11.7)
History of PID	
No	201 (90.5)
Yes	21 (9.5)
History of Tubal Surgery	
No	214 (96.4)
Yes	8 (3.6)
History of Pelvic surgery	
No	202 (91)
Yes	20 (9)
PCOS Diagnosis	
No	146 (65.8)
Yes	76 (34.2)

BMI: Body mass index; PCOS: Polycystic ovary syndrome; PID: Pelvic inflammatory disease

RESULTS

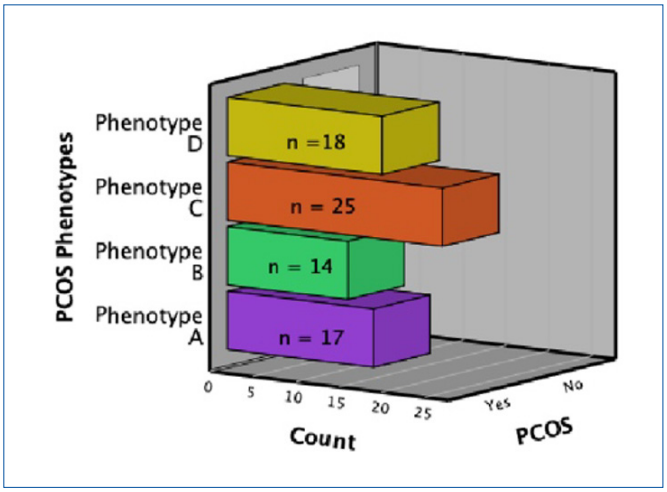
Table 1 presents the demographic and clinical characteristics of the study population, which included 222 women aged between 19 and 43 years. Among them, 76 (34.2%) were in the PCOS group, while 146 (65.8%) were in the non-PCOS group. Comparison between the two groups revealed that the non-PCOS group had a significantly higher prevalence of PID (18 vs. 3, $p = 0.043$) and prior pelvic surgeries (19 vs. 1, $p = 0.004$). Additionally, smoking prevalence was significantly higher in the non-PCOS group (41.8% vs. 23.7%, $p = 0.008$). None of the women in the study received infertility treatment. No significant difference was observed between the groups in terms of overall history of ectopic pregnancy or the number of previous ectopic pregnancies and presence of IUD. However, the incidence of ectopic pregnancy during the first pregnancy was significantly higher in the PCOS group (Table 2).

In the PCOS group, the most commonly reported feature was polycystic ovarian morphology, observed in 78.9% of women, followed by clinical or biochemical hyperandrogenism in 75% and oligo-/anovulation in 64.5%. Based on these features, the women were classified into four phenotypes: 17 women were classified

Table 2. Comparison of Demographic and Clinical Characteristics Between Non-PCOS and PCOS Groups

	non-PCOS group (n= 146)	PCOS group (n= 76)	p
Age (y) (mean±SD)	30.47±4.36	30.18±4.97	0.657
BMI (kg/m²) (mean±SD)	25.82±4.37	24.5±4.21	**0.032**
Infertility time (month) (median,min-max)	4.79±10.12	9.39±18.36	**0.045**
Gravidity (median,min-max)	3 (1-7)	3 (1-5)	0.324
Parity (median,min-max)	1 (0-4)	1 (0-2)	0.621
Abortus (median,min-max)	1 (0-3)	1 (0-2)	0.231
	N (%)		
History of Ectopic pregnancy			0.234
no	85 (58.2)	36 (47.4)	
1 time	56 (38.4)	35 (46.1)	
2 times	5 (3.4)	5 (6.6)	
History of Ectopic Pregnancy in the First Pregnancy			**<0.001**
No	129 (88.4)	48 (63.2)	
Yes	17 (11.6)	28 (36.8)	
Smoking			**0.008**
No	85 (58.2)	58 (76.3)	
Yes	61 (41.8)	18 (23.7)	
Presence of Intrauterine Device			0.086
No	134 (91.8)	74 (97.4)	
Yes	12 (8.2)	2 (2.6)	
History of PID			**0.043**
No	128 (87.7)	73 (96.1)	
Yes	18 (12.3)	3 (3.9)	
History of Tubal Surgery			0.843
No	141 (96.6)	73 (96.1)	
Yes	5 (3.4)	3 (3.9)	
History of Pelvic surgery			**0.004**
No	127 (87)	75 (98.7)	
Yes	19 (13)	1 (1.3)	

BMI: Body mass index; PCOS: Polycystic ovary syndrome; PID: Pelvic inflammatory disease



as Phenotype A, 14 as Phenotype B, 25 as Phenotype C, and 18 as Phenotype D (Figure 2). When comparing the phenotypes, no significant differences were found in terms of age, BMI, duration of infertility, history of PID or the presence of IUD. The prevalence of ectopic pregnancy during the first pregnancy varied across the phenotypes: 41.2% in Phenotype A (n=7), 57.1% in Phenotype B (n=8), 20% in Phenotype C (n=5), and 33.3% in Phenotype D (n=6).

Figure 2. Distribution of Women Across PCOS Phenotypes (Phenotype A includes clinical or biochemical hyperandrogenism, oligo-/anovulation, and polycystic ovarian morphology (PCOM); Phenotype B comprises hyperandrogenism along with oligo-/anovulation; Phenotype C includes hyperandrogenism and PCOM; and Phenotype D is characterized by oligo-/anovulation combined with PCOM)

Table 3. Logistic Regression Analysis of PCOS and PCOS Phenotypes for the Association with Ectopic Pregnancy During the First Pregnancy

Variable		ß	Lower 95% CI	Upper 95% CI	p
PCOS diagnosis	No	ref	-	-	-
	Yes	4.42	2.22	8.8	**< 0.001**
Phenotype A		4.75	1.61	13.98	**0.005**
Phenotype B		9.05	2.83	28.96	**< 0.001**
Phenotype C		1.69	0.57	5.05	0.342
Phenotype D		3.39	1.13	10.11	**0.028**

PCOS: Polycystic ovary syndrome

The diagnosis of PCOS was found to be 4.42 times more likely to be associated with ectopic pregnancy during the first pregnancy (OR: 4.42, 95% CI: 2.22–8.80, $p < 0.001$). When examining the PCOS phenotypes, Phenotypes B, A, and D were found to be associated with an increased likelihood of ectopic pregnancy during the first pregnancy (Table 3). However, none of the other variables, including age, BMI, smoking status, history of PID, history of tubal or pelvic surgery, or the presence of IUD, were found to be significantly associated with ectopic pregnancy during the first pregnancy.

DISCUSSION

The findings indicate that women with PCOS may be at an elevated risk for ectopic pregnancy, especially during their first pregnancy. This elevated risk highlights a potentially significant, but understudied, area in reproductive medicine—how PCOS-related hormonal and structural alterations may influence tubal function and, consequently, pregnancy location.

PCOM was the most common feature in the PCOS group (78.9%), followed by clinical or biochemical hyperandrogenism (75%) and oligo-/anovulation (64.5%). These findings are consistent with previous research showing that PCOM is a key feature of PCOS and is linked to hormonal imbalances and ovulatory dysfunction (21). Ozel et al. found a significant association between PCOM and ectopic pregnancy, suggesting PCOM could serve as an early indicator of increased risk for ectopic pregnancies (7).

Different PCOS phenotypes may uniquely influence tubal health. In our study, women with Phenotypes C and D exhibited a lower prevalence of ectopic pregnancy during their first pregnancy. This finding aligns with a study by Ghobrial et al. who showed that women with these phenotypes had a lower likelihood of tubal occlusion (5). These phenotypes may be associated with a reduced risk of tubal damage and ectopic pregnancy.

Research on the impact of testosterone on fallopian tubes suggests that elevated androgen levels—common in PCOS—can impair ciliary function and disrupt embryo transport, thereby increasing the risk of ectopic pregnancy (22). In another study examining testosterone exposure, changes such as ciliary clumping and partial luminal blockage were observed, which might increase the risk of tubal occlusion and ectopic pregnancy (23). These findings support the hypothesis that hyperandrogenism impacts both ovarian morphology and tubal function. Interestingly, Mayrhofer et al. did not observe significant differences in tubal occlusion between women with PCOS and controls, suggesting that PCOS might not always impair tubal patency, especially in medication-resistant anovulation cases (6).

Although our study found that non-PCOS women had higher rates of PID, prior surgeries, smoking, and IUD use—known contributors to tubal dysfunction—our results suggest that the hormonal milieu in PCOS may be a more significant factor in increasing ectopic pregnancy risk during the first pregnancy. This underscores the need for more focused investigation of PCOS-related tubal changes beyond traditional risk factors.

One of the key strengths of this study is the single-center diagnosis of PCOS, which enhances the reliability and consistency of the data. By diagnosing all participants within the same clinical setting, we were able to ensure a standardized approach, reducing variability in the diagnostic process and strengthening the validity of the findings. Despite adjusting for potential confounders, there may be other unmeasured factors that could still influence the results. Given the retrospective nature of this study, we acknowledge that causality cannot be conclusively determined. Further prospective studies are recommended to validate our findings and clarify the

mechanisms underlying the relationship between PCOS and tubal ectopic pregnancy. Additionally, multi-center studies are needed to validate these results in broader populations.

CONCLUSIONS

Our findings indicate that women with PCOS may be at an increased risk for ectopic pregnancy, particularly during their first pregnancy, likely due to altered tubal patency and reduced ciliary function. These results emphasize the need for further prospective studies to explore the specific mechanisms through which hormonal imbalances in PCOS affect fallopian tube function. Targeted interventions may be beneficial in reducing the risk of ectopic pregnancy in this population. Additionally, our findings highlight the importance of targeted fertility counseling and management strategies for women diagnosed with PCOS. Regular hormonal evaluations, fertility counseling, and close monitoring during early pregnancy could be beneficial in mitigating the risk of tubal ectopic pregnancies.

Author Contributions

Conceptualization: B.K, Data Curation: S.M., S.K.E, Formal Analysis: B.K., C.K, Investigation: B.K., S.M., S.K.E, Methodology: B.K., C.K., S.M, Project Administration: B.K,, S.K.E, Supervision: C.K, Writing – Original Draft: B.K, Writing – Review & Editing: B.K., C.K.

Conflict of Interest

Authors declare no conflict of interest.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Comparative outcomes of transobturator tape and tension-free vaginal tape procedures in mixed urinary incontinence: a retrospective cohort study

Miks üriner inkontinans cerrahi tedavisinde transobturator tape ve tension-free vaginal tape prosedürlerinin karşılaştırmalı sonuçları: Retrospektif kohort çalışması

Fatih KILIÇ[1,2], Can TERCAN[3], Ali Selçuk YENİOCAK[3], Mahmut Kuntay KOKANALİ[2], Hüseyin YEŞİLYURT[2]

[1]Department of Obstetrics and Gynecology, Merkezefendi State Hospital, Manisa, Türkiye
[2]Department of Obstetrics and Gynecology, Ankara City Hospital, Ankara, Türkiye
[3]Department of Obstetrics and Gynecology, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye

ABSTRACT

Aim: This study aimed to compare the outcomes of Transobturator Tape (TOT) and Tension-Free Vaginal Tape (TVT) procedures in the treatment of Mixed Urinary Incontinence (MUI), focusing on objective and subjective cure rates, postoperative complications, and quality of life improvements.

Materials and Methods: A retrospective cohort study was conducted at a tertiary hospital specializing in women's health and education between January 2014 and June 2018. Seventy patients diagnosed with MUI underwent either TOT (n=38) or TVT (n=32) procedures. Preoperative and postoperative data were collected, including demographics, urodynamic parameters, and validated quality of life questionnaires (UDI-6 and IIQ-7). Objective cure was defined as a negative cough stress test and no need for incontinence medication. Subjective cure was determined by UDI-6 scores. Statistical analysis was performed to evaluate outcomes and identify factors affecting surgical success.

Results: Both TOT and TVT procedures significantly improved quality of life, with no significant difference in objective cure rates (68.4% vs. 65.6%, p=0.804) or postoperative complications between the two groups. Urethral mobility was identified as a positive predictor of objective cure (OR 1.1, p=0.020), while detrusor overactivity negatively impacted surgical success (OR 1.1, p=0.031). Both procedures demonstrated similar efficacy in treating the stress and urge components of MUI.

Conclusions: TOT and TVT are equally effective and safe for the short-term treatment of MUI, with low complication rates. Urethral mobility and detrusor overactivity are important factors influencing surgical outcomes. Further large-scale, prospective studies are needed to confirm these findings and optimize patient selection for these procedures.

Keywords: Mixed urinary incontinence, quality of life scales, tension-free vaginal tape, transobturator tape

ÖZ

Amaç: Bu çalışmanın amacı, Miks Üriner İnkontinans (MÜİ) tedavisinde Transobturator Tape (TOT) ve Tension-Free Vaginal Tape (TVT) prosedürlerinin sonuçlarını karşılaştırmaktır. Çalışma, objektif ve subjektif kür oranları, postoperatif komplikasyonlar ve yaşam kalitesindeki iyileşmeleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Ocak 2014 ile Haziran 2018 tarihleri arasında üçüncü basamak bir kadın sağlığı eğitim ve araştırma hastanesinde retrospektif kohort tasarımında gerçekleştirilmiştir. MÜİ tanısı konulan 70 hasta TOT (n=38) veya TVT (n=32) prosedürleri ile tedavi edilmiştir. Preoperatif ve postoperatif veriler toplanmış; demografik özellikler, ürodinamik parametreler ve yaşam kalitesi anketleri (UDI-6 ve IIQ-7) kullanılmıştır. Objektif kür, negatif öksürük stres testi ve inkontinans nedenli medikal tedavi ihtiyacı olmaması şeklinde tanımlanmıştır. Subjektif kür ise UDI-6 skorları ile belirlenmiştir. Cerrahi başarıyı değerlendirmek ve etkileyen faktörleri belirlemek için uygun istatistiksel analizler yapılmıştır.

Bulgular: TOT ve TVT prosedürlerinin her ikisi de yaşam kalitesini anlamlı derecede iyileştirmiştir, Her iki grup arasında objektif kür oranlarında (%68,4 vs. %65,6, p=0,804) veya postoperatif komplikasyonlarda anlamlı bir fark bulunmamıştır. Üretral mobilite, objektif kür için pozitif bir belirleyici olarak saptanmıştır (OR 1,1, p=0,020), buna karşın detrüsör aşırı aktivitesi cerrahi başarıyı olumsuz etkilemiştir (OR 1,1, p=0,031). Her iki prosedür de MÜİ'nin stres ve urgency bileşenlerinin tedavisinde benzer etkinlik göstermiştir.

Sonuç: TOT ve TVT, MÜİ'nin kısa dönem tedavisinde eşit derecede güvenli ve etkili olmakla birlikte düşük komplikasyon oranlarına sahiptir. Üretral mobilite ve detrüsör aşırı aktivitesi cerrahi sonuçları etkileyen önemli faktörlerdir. Bu bulguları doğrulamak ve bu prosedürler için hasta seçimini optimize etmek amacıyla daha geniş ölçekli, prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Miks üriner inkontinans, tension-free vaginal tape, transobturator tape, yaşam kalitesi ölçekleri

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Sorumlu Yazar/Corresponding Author: Can TERCAN, Department of Obstetrics and Gynecology, Basaksehir Cam and Sakura City Hospital, İstanbul, Türkiye
E-mail: cntrcn89@gmail.com

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INTRODUCTION

Mixed urinary incontinence (MUI) is a prevalent condition characterized by the involuntary leakage of urine, associated with both stress and urgency incontinence (1). This dual manifestation makes MUI a complex and challenging condition to manage, as it encompasses symptoms of both stress urinary incontinence (SUI) and urge urinary incontinence (UUI). The burden of MUI significantly impacts the quality of life of affected women, leading to diminished quality of life, psychological distress, and reduced physical activity (2,3).

Surgical intervention, particularly mid-urethral sling (MUS) procedures, has become the cornerstone of treatment for women with MUI who do not respond adequately to conservative management (4). Among the MUS procedures, the Transobturator Tape (TOT) and Tension-Free Vaginal Tape (TVT) techniques are widely used. Both approaches aim to provide support to the urethra, thereby reducing or eliminating involuntary urine leakage (5). The TOT procedure, introduced by Delorme in 2001, involves the placement of a synthetic sling through the obturator foramen, whereas the TVT procedure, introduced by Ulmsten in 1996, involves the placement of the sling via a retropubic approach (6,7).

MUI involves both stress and urgency incontinence, reflecting mechanisms from the integral and hammock theories. The integral theory, emphasizes the pubourethral ligament, suburethral hammock, and pelvic floor muscles in urethral closure (8). Weakness in these can lead to inappropriate micturition reflexes and UUI, while affecting suburethral support results in SUI. DeLancey's hammock theory focuses on the pubocervical fascia and its connection to the levator ani muscles (9). Weakened support, especially under increased intra-abdominal pressure, can cause urethral displacement and SUI. TOT and TVT procedures aim to restore urethral support by reinforcing these structures, addressing MUI causes.

Despite their widespread use, the relative effectiveness and safety of TOT and TVT in the management of MUI remain subjects of ongoing debate. Various studies have reported conflicting results regarding the comparative outcomes of these procedures, particularly in terms of objective and subjective cure rates, postoperative complications, and patient-reported quality of life (10). Furthermore, the influence of preoperative factors, such as urethral mobility and detrusor overactivity, on surgical outcomes has yet to be fully elucidated.

Given these uncertainties, the present study aims to compare the outcomes of TOT and TVT procedures in a cohort of patients diagnosed with MUI. Specifically, we seek to evaluate the objective and subjective cure rates, postoperative complications, and quality of life outcomes associated with each procedure. Additionally, we aim to identify preoperative factors that may influence the success of these surgical interventions.

By providing a comprehensive comparison of TOT and TVT in the context of MUI, this study seeks to contribute to the existing body of knowledge and assist clinicians in making informed decisions regarding the optimal surgical approach for their patients.

MATERIALS AND METHODS

Study Design

Retrospective cohort study included patients who presented with involuntary urinary incontinence at the Urogynecology Clinic of a tertiary hospital specializing in women's health between January 2014 and June 2018, after obtaining ethical approval from the local Clinical Research Ethics Committee (Approval No: 50/2018, dated 26.09.2018). These patients underwent mid-urethral sling surgery, either TOT or TVT, and were diagnosed with MUI based on preoperative history, examination findings, and urodynamic confirmation.

Setting

The study was conducted at the Urogynecology Clinic of a tertiary hospital. Data were collected retrospectively from hospital archives covering patients treated between January 2014 and June 2018. All eligible patients meeting the inclusion criteria within the specified period were included in the study.

Participants

Patients diagnosed with MUI, confirmed through preoperative history, physical examination, and urodynamic studies. MUI-positive patients were defined as those with complaints of urine leakage during coughing or sneezing and urgency incontinence symptoms, positive cough stress test results on examination, and urodynamic evidence of detrusor overactivity during filling cystometry and a positive urodynamic stress test.

Patients were excluded if they had previously undergone pelvic organ prolapse (POP) surgery and/or anti-incontinence surgery, had comorbid conditions such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), hypertension, neurological or psychiatric disorders, insufficient data, or had undergone prior medical treatment for incontinence. Patients with advanced-stage POP (grad-2 and above) or those who did not consent to participate were also excluded.

Variables

The primary outcomes were the objective and subjective cure rates of MUS surgery at six months postoperatively. Objective cure was defined as a negative cough stress test and the absence of any need for medication for incontinence. Subjective cure was defined as a score of ≤1 on the second and third questions of the UDI-6 form. ("Do you experience urine leakage associated with a feeling of urgency and if so, how much does it bother you?") and third question ("Do you experience urine leakage related to physical activity, coughing, or sneezing, and if so, how much does it bother you?") of the UDI-6 form (10).

Data Sources/Measurement

Data were extracted from the patients' preoperative and postoperative records, including age, height, weight, obstetric history, body mass index (BMI), comorbidities, history of pelvic and urogynecological surgeries, smoking status, and current medications. The preoperative evaluation included urodynamic studies, post-void residual urine volume measured by urinary catheterization, and POP grading using the Baden-Walker classification system.

Patients underwent MUS surgery (TOT or TVT) performed by the same experienced urogynecological team using macroporous polypropylene mesh materials (Düzey SVT Vaginal Tape Mesh, Düzey Medical, Turkey). The type of anesthesia, operation time, and any complications were recorded. Postoperative evaluations were conducted at six months, including urogynecological examination findings and validated Turkish versions of the IIQ-7 and UDI-6 quality of life questionnaires (11).

Bias

Selection bias was minimized by rigorously applying inclusion and exclusion criteria and by using standardized methods for data collection and patient evaluation.

Statistical Methods

SPSS 17.0 (Statistical Package for Social Sciences) software was used for statistical analyses. Multiple logistic regression analysis was employed to identify significant risk factors affecting objective cure. Odds ratios (OR), 95% confidence intervals (CI), and significance levels were calculated.

Quantitative Variables

Continuous variables were assessed for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation and analyzed using the independent t-test. Non-normally distributed data were presented as median (minimum-maximum) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages, analyzed using the chi-square test. Statistical significance was set at p-value<0.05.

RESULTS

Of the 70 participants, 38(54.3%) underwent the TOT procedure, and 32(45.7%) underwent the TVT procedure. Demographic and preoperative clinical characteristics were recorded and analyzed (Table 1). The mean age was significantly higher in the TOT group compared to the TVT group (53.4±9.02 vs. 47.4±6.8 years, p=0.012). Both groups had similar gravidity and parity, and the majority of patients in both groups were multiparous (89.5% in TOT vs. 78.1% in TVT, p=0.194). BMI and the prevalence of obesity were comparable between the groups (30.3±3.2 vs. 29.6±3.8 kg/m², p=0.414). Additionally, there was no significant difference in menopause status, smoking history, or history of macrosomic birth between the groups.

Urethral mobility was notably higher in the TOT group (94.7% vs. 62.5%, p=0.001). However, other urodynamic parameters, such as residual urine volume, maximum cystometric capacity, and preoperative valsalva leak point pressure (VLPP) and maximal urethral closure pressure (MUCP) values, showed no significant differences between the two groups. The presence of grade-1 cystocele, rectocele, and uterine descent were also similar between the groups.

Postoperative outcomes were assessed using the UDI-6 and IIQ-7 quality of life scales (Table 2). Both groups showed significant improvements in their scores postoperatively, with no significant differences between the groups in terms of improvement magnitude or complication rates. Objective and subjective cure rates showed no significant difference between the groups, with 68.4% of TOT patients achieving objective cure versus 65.6% in the TVT group (p=0.804).

Further analysis of the UDI-6 scores revealed a significant reduction in the severity of symptoms postoperatively for both procedures (Table 3). For the TOT procedure, 50% of patients reported no symptoms for UDI-6 Question 2 postoperatively, compared to 0% preoperatively (p<0.001). Similarly, the TVT group saw a significant increase in patients reporting no symptoms for the same question (40.6% postoperatively vs. 0% preoperatively, p<0.001). Both groups also showed significant improvements in UDI-6 Question 3 scores, with a marked reduction in severe symptoms postoperatively.

Table 1. Demographic and Preoperative Clinical Characteristics of the Groups

	TOT (N=38)	TVT (N=32)	p-value
Age (Years)	53.4 ± 9.02	47.4 ± 6.8	**0.012**
Follow-up Duration (Months)	6.3 ± 0.7	6.2 ± 0.6	0.843
Gravidity	3 (1-6)	3 (1-8)	0.912
Parity	2 (1-6)	2 (1-7)	0.879
Multiparity (%)	34 (89.5)	25 (78.1)	0.194
Primiparity (%)	4 (10.5)	7 (21.9)	0.194
BMI (kg/m²)	30.3 ± 3.2	29.6 ± 3.8	0.414
Obesity (≥30 kg/m²) (%)	10 (20.3)	8 (25.0)	0.900
Menopause Presence (%)	21 (55.3)	13 (40.6)	0.222
History of Macrosomic Birth (%)	5 (13.2)	6 (18.8)	0.522
Smoking (%)	5 (13.2)	7 (21.9)	0.335
Positive CST (%)	35 (92.1)	30 (93.8)	0.790
Urethral Mobility Presence (%)	36 (94.7)	20 (62.5)	**0.001**
Grade 1 Cystocele (%)	24 (63.2)	18 (56.3)	0.557
Grade 1 Rectocele (%)	20 (52.6)	18 (56.3)	0.762
Grade 1 Uterine Descent (%)	8 (21.1)	6 (18.8)	0.810
Residual Urine Volume (cc)	80.6 ± 10.4	78.5 ± 9.7	0.638
Maximum Cystometric Capacity (cc)	400 (320-420)	430 (360-450)	0.329
VLPP (cmH_2O)	79.1 ± 12.1	70.6 ± 10.4	0.168
MUCP (cmH_2O)	50.6 ± 5.8	44.8 ± 10.2	0.102
Presence of DO (%)	27 (71.1)	22 (68.8)	0.834
Operation Duration (min)	45.8 ± 12.6	44.9 ± 11.6	0.818

Data are presented as mean ± standard deviation, median (minimum - maximum), or number (%).

BMI: Body Mass Index; CST: Cough Stress Test; DO: Detrusor Overactivity, IIQ-7: Incontinence Impact Questionnaire-7, MUCP: Maximal Urethral Closure Pressure VLPP: Valsalva Leak Point Pressure, UDI-6: Urogenital Distress Inventory-6.

Table 2. Preoperative and Postoperative Quality of Life Scores

	TOT (N=38)	TVT (N=32)	p-value
Preop. UDI-6	13.5 ± 3.4	14.1 ± 3.4	0.623
Preop. IIQ-7	15.6 ± 3.7	16.1 ± 3.0	0.418
Postop UDI-6 Score	3.2 ± 0.9	3.3 ± 1.1	0.836
Change in UDI-6 Score	10.6 ± 3.9	11.0 ± 3.5	0.614
Postop IIQ-7 Score	3.9 ± 1.0	3.3 ± 1.0	0.416
Change in IIQ-7 Score	11.9 ± 4.1	12.7 ± 3.8	0.783
Objective Cure (%)	26 (68.4)	21 (65.6)	0.804
Subjective Cure (%)	28 (73.7)	21 (65.6)	0.464
Postop Stress Test (+) (%)	5 (13.2)	3 (9.4)	0.620
Postop Medication (+) (%)	10 (26.3)	11 (34.4)	0.464
Complication: Bladder Perforation (%)	0 (0)	1 (3.1)	-
Complication: Voiding Dysfunction (%)	1 (2.6)	2 (6.3)	-
Complication: Erosion (%)	1 (2.6)	-	-

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

DO: Detrusor Overactivity, IIQ-7: Incontinence Impact Questionnaire-7, MUCP: Maximal Urethral Closure Pressure, UDI-6: Urogenital Distress Inventory-6.

Multiple regression analysis was conducted to identify factors related to achieving an objective cure (Table 4). Urethral mobility was positively associated with an objective cure (OR 1.1, p=0.020), while the presence of detrusor overactivity was associated with a decreased likelihood of achieving an objective cure (OR 1.1, p=0.031). Other factors, including age, parity, obesity, menopause status, preoperative VLPP, preoperative MUCP, and the type of procedure (TOT vs. TVT), were not significantly associated with objective cure outcomes.

Table 3. Distribution of UDI-6 Quality of Life Scale Scores Preoperatively and Postoperatively for TOT and TVT Procedures

UDI-6 Scale - Question 2 Score	Preoperative	Postoperative	p-value
TOT Procedure			
0 (None)	0 (0.0%)	19 (50.0%)	**<0.001**
1 (Mild)	2 (5.3%)	9 (23.7%)	**<0.001**
2 (Moderate)	12 (31.6%)	4 (10.5%)	**<0.001**
3 (Severe)	24 (63.2%)	6 (15.8%)	**<0.001**
TVT Procedure			
0 (None)	0 (0.0%)	13 (40.6%)	**<0.001**
1 (Mild)	1 (3.1%)	8 (25.0%)	**<0.001**
2 (Moderate)	9 (28.1%)	4 (12.5%)	**<0.001**
3 (Severe)	22 (68.8%)	7 (21.9%)	**<0.001**
UDI-6 Scale - Question 3 Score	**Preoperative**	**Postoperative**	**p-value**
TOT Procedure			
0 (None)	0 (0.0%)	30 (78.9%)	**<0.001**
1 (Mild)	4 (10.5%)	3 (7.9%)	**<0.001**
2 (Moderate)	12 (31.6%)	1 (2.6%)	**<0.001**
3 (Severe)	21 (55.3%)	4 (10.5%)	**<0.001**
TVT Procedure			
0 (None)	1 (3.1%)	27 (84.4%)	**<0.001**
1 (Mild)	2 (6.3%)	2 (6.3%)	**<0.001**
2 (Moderate)	3 (9.4%)	1 (3.1%)	**<0.001**
3 (Severe)	26 (81.3%)	2 (6.3%)	**<0.001**

Data are presented as number (%).
IIQ-7: Incontinence Impact Questionnaire-7, UDI-6: Urogenital Distress Inventory-6.

Table 4. Multiple Regression Analysis Results for Factors Related to Objective Cure

Factor	Objective Cure Present (N=47)	No Objective Cure (N=23)	OR (95% CI)	p-value
Age (Years)	50.1 ± 8.2	51.1 ± 7.4	1.1 (0.1-9.5)	0.912
Parity	2 (1-6)	2 (1-7)	1.1 (0.2-10.5)	0.941
Obesity	12 (25.5%)	6 (26.1%)	0.9 (0.3-11.5)	0.818
Menopause	22 (46.9%)	12 (52.2%)	0.6 (0.2-13.0)	0.799
Urethral Mobility	42 (89.4%)	14 (60.9%)	1.1 (1.0-1.2)	0.020
Preoperative VLPP (cmH2O)	69.2 ± 11.2	70.1 ± 10.2	1.4 (1.0-2.7)	0.679
Preoperative MUCP (cmH2O)	49.8 ± 6.3	44.3 ± 5.7	0.8 (0.6-1.4)	0.565
TOT	26 (55.3%)	12 (52.2%)	1.2 (0.5-18.3)	0.729
TVT	21 (44.7%)	11 (47.8%)	1.2 (0.5-18.3)	0.729
DO Present	30 (63.8%)	19 (82.6%)	1.1 (1.1-1.2)	**0.031**

Data are presented as mean ± standard deviation, median (range), or number (%). OR: Odds Ratio, CI: Confidence Interval,
DO: Detrusor Overactivity, MUCP: Maximal Urethral Closure Pressure, VLPP: Valsalva Leak Point Pressure.

In summary, the TOT and TVT procedures both resulted in significant improvements in quality of life, as measured by UDI-6 and IIQ-7 scores, with no significant differences in complication rates or cure rates between the two techniques. Urethral mobility emerged as a significant factor in achieving an objective cure, whereas detrusor overactivity negatively impacted the likelihood of success.

DISCUSSION

The treatment of MUI, encompassing both SUI and UUI, requires a multifaceted approach involving conservative, surgical, and medical options. There is no consensus on the optimal treatment approach for MUI, necessitating individualized treatment plans that may involve a combination of therapies.

The Petros Integral Theory highlights the role of lax suspensory ligaments in pelvic floor dysfunction, classifying three anatomical 'zones' based on ligament locations. The anterior zone, from the external meatus to the bladder neck, includes the external urethral ligament (EUL), pubourethral ligament (PUL), and vaginal 'hammock.' The middle zone, from the bladder neck to the cervix, contains the arcus tendineus fascia pelvis (ATFP), cardinal ligaments, and pubocervical fascia (PCF). The posterior zone, from the cervix to the perineal body, includes the uterosacral ligaments (USL), perineal body (PB), and rectovaginal fascia (RVF). The uterus contributes to both the middle and posterior zones via the cervical rings. Surgically, the theory supports minimally invasive procedures to address lax ligaments causing prolapse or symptoms. A less invasive tensioned sling, developed in 2005, reinforces all four suspensory ligaments and the perineal body, reattaching organs to the levator hiatus. It is often preferred for young, sexually active women without urethral mobility. (12)

Our study, aiming to evaluate the effectiveness of TOT versus TVT procedures in treating MUI, found that the average age of patients in the TVT group was significantly lower than that in the TOT group (p=0.012). This aligns with general urogynecological practice, where TVT is preferred for younger patients to reduce the incidence of complications such as dyspareunia and mesh erosion (13). Older patients tend to undergo TOT due to its lower surgical morbidity. This demographic difference reflects the clinical approach to selecting surgical procedures for MUI.

Preoperative clinical characteristics revealed a significantly higher rate of urethral hypermobility in the TOT group compared to the TVT group (94.7% vs. 62.5%, p=0.001). This preference for TOT in cases of urethral hypermobility and TVT in cases without such mobility reflects the clinical belief that TOT offers similar efficacy with a lower risk of severe complications (14). This approach is consistent with recommended practices in urogynecology.

The effectiveness of surgical methods for treating MUI is not well-defined in the literature due to varying impacts on the stress and urge components of MUI. While surgery is generally considered effective for improving the stress component, its impact on urge symptoms is less clear, with some studies suggesting that urge symptoms might worsen postoperatively (13). Our study found significant improvements in both stress and urge components following MUI surgeries.

Previous studies have reported varying outcomes for urge symptoms after different surgical procedures. For instance, Tahseen et al. (2009) found a 79% improvement in urge symptoms after TOT surgery (15). Kulseng-Hanssen et al. (2008) observed that 43% of patients had complete resolution of urge symptoms at 7 months post-TVT operation, with 34.6% at 38 months (16). Our study showed that 34.4% of patients in the TVT group and 26.3% in the TOT group required postoperative medication for urge symptoms at 6 months, suggesting that TVT might result in relatively less improvement in urge symptoms, though this difference was not statistically significant.

Other studies, such as those by Segal et al. (2004) and Paick et al. (2004), found high success rates for both stress and urge components with TVT and TOT procedures (17,18).

Kudish et al. (2010) reported similar high success rates for both procedures, while Nyssönen et al. (2014) and Jain et al. (2010) found no significant difference in effectiveness between TVT and TOT in treating MUI symptoms. (13,19,20). However, Salo et al. (2023) found no significant difference in the effectiveness of the two procedures for treating SUI, even in the long-term follow-up period (21). Our findings support the literature, indicating that both TOT and TVT procedures are similarly effective in treating stress incontinence, with no significant difference in objective cure rates.

Complication rates also differ between procedures. TOT is generally considered safer with fewer major complications compared to TVT, which is associated with a higher incidence of major organ injuries, bladder perforation, and postoperative voiding dysfunction (22). Our study found low complication rates for both procedures, with similar occurrences of adverse events, supporting the safety of both approaches (23).

The literature on factors affecting surgical success for MUI is limited. Some studies suggest that preoperative low Maximum Urethral Closure Pressure (MUCP), presence of detrusor overactivity, and history of previous anti-incontinence surgery may negatively impact surgical outcomes (18,24,25). Our study focused on the effectiveness of TOT and TVT, excluding these potential risk factors, thus not categorizing them as risk factors. However, factors such as immobile urethra and presence of detrusor overactivity were found to negatively affect surgical success in our study.

Our study's limitations include its retrospective design and small sample size, which restrict generalizability. Additionally, short-term outcomes necessitate further investigation in long-term studies. The lack of consensus in defining UUI within MUI may also affect the comparison of our results with existing literature. Despite these limitations, our study contributes valuable insights into the comparative effectiveness of TOT and TVT for MUI and underscores the need for larger, prospective, randomized studies to confirm these findings and enhance clinical practice.

CONCLUSION

Both TOT and TVT procedures are effective in the short term for treating both stress and urge incontinence in MUI. There is no significant difference in effectiveness between the two methods. Both procedures have low complication rates, making them safe options. However, preoperative factors such as immobile urethra and detrusor overactivity may reduce the success rate of these operations. Informing patients about these factors is crucial for ensuring they are well-informed, which in turn helps build trust, especially in cases where the outcomes may be less favorable. Further prospective, randomized studies are needed to validate these results and optimize clinical practice.

Conflict of interest
None

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Servikal sitolojisi ASC-H olan hastalarda histolojik CIN2+ lezyonları öngörebilir miyiz?

Can we predict histological CIN2+ lesions in patients with ASC-H cervical cytology?

Saliha SAGNİC[1], Fatma Ceren GÜNER[1], Merve Gül KARA[2], Sefa Metehan CEYLAN[2], Hasan Aykut TUNCER[1], Selen DOĞAN[1], Tayup SİMSEK[1]

[1]Akdeniz Üniversitesi Tıp fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Kliniği, Antalya, Türkiye
[2]Akdeniz Üniversitesi Tıp fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Antalya, Türkiye

ÖZ

Amaç: Bu çalışmanın amacı servikal sitolojide yüksek dereceli squamöz intraepitelyal lezyon dışlanamayan atipik skuamöz hücreler (ASC-H) saptanan hastalarda, histolojide servikal intraepitelyal lezyon grade 2 ve üzeri (CIN2+) lezyonları saptamada rol alan faktörleri ortaya koymaktır.

Gereç ve Yöntemler: 2014-2023 yıllarında servikal sitoloji sonucu ASC-H olup kolposkopi ile değerlendirilen 98 hasta bu kesitsel çalışmaya dahil edildi. Hastaların klinik ve patolojik özellikleri medikal dosyalarından retrospektif olarak kaydedildi. Altta yatan CIN2+ lezyonu öngörmek için belirlenen risk faktörlerine yönelik çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Çalışma popülasyonun %40,8'inde ≥CIN2+ lezyon saptandı. Regresyon analizinde değerlendirilen on üç tane değişken arasından sadece yüksek riskli Human Papilloma Virüs (hrHPV) testinin pozitif saptanması ve hastanın semptomatik olması, ≥CIN2+ lezyonunun öngörülmesine önemli ölçüde katkıda bulunmuştur. hrHPV testinin pozitif saptandığı hastaların, HPV negatif bireylere göre CIN2+ tanısı alma olasılığının yaklaşık 8,6 kat daha yüksek olduğu görülmüştür. Semptomatik bireylerin CIN2+ sonuçlarına sahip olma olasılığının 3,355 kat daha fazla olduğu saptanmıştır.

Sonuç: Servikal sitolojisi ASC-H olan hastalarda, hrHPV testinin pozitif olması ve semptom varlığı CIN2+ varlığını öngörmede önemli faktörlerdir. ASC-H sitolojisinin yönetiminde hastaların klinik ve patolojik özellikleri göz önünde bulundurularak daha detaylı bir yaklaşım tavsiye edilebilir.

Anahtar Kelimer: Yüksek dereceli squamöz intraepitelyal lezyon dışlanamayan atipik skuamöz hücreler, ASC-H, Human Papilloma Virüs, Servikal intraepithelyal neoplazi; Serviks kanseri

ABSTRACT

Aim: The aim of this study is to reveal the factors involved in detecting cervical intraepithelial lesion grade 2 and more significiant (CIN2+) lesions in patients with atypical squamous cells in which high-grade squamous intraepithelial lesion cannot be excluded (ASC-H) in cervical cytology.

Materials and Methods: Ninety eight patients with ASC-H smears who were evaluated with colposcopy from 2014 to 2023 were included in this cross-sectional study. The clinicopathological characteristics of the patients were examined retrospectively. Multivariate logistic regression analysis was performed for the identified risk factors to predict the underlying CIN2+ lesion.

Results: ≥CIN2+ lesions were detected in 40.8% of the study cohort. Of the thirteen variables evaluated in the regression analysis, only a positive high risk Human Papilloma Virüs (hrHPV) test and the presence of symptoms contributed significantly to the prediction of ≥CIN2+ lesion. It has been noticed that patients with a positive hrHPV test are approximately 8.6 times more likely to be diagnosed with CIN2+ than HPV-negative individuals. Symptomatic individuals were detected to be 3,355 times more likely to have CIN2+ results.

Conclusion: A positive hrHPV test and the presence of symptoms are important factors in predicting histological CIN2+ in patients with ASC-H cytology. A more detailed approach in the management of ASC-H cytology may be recommended, taking into account the clinical and pathological characteristics of the patients.

Keywords: Atypical squamous cells; cannot exclude high-grade squamous intraepithelial lesion; ASC-H, Human Papilloma Virus, Cervical intraepithelial neoplasia; Cervical cancer

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Sorumlu Yazar/Corresponding Author: Saliha SAĞNIÇ, Akdeniz Üniversitesi Tıp fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Kliniği, Antalya, Türkiye
E-mail: drsalihasagnic@hotmail.com

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GİRİŞ

Servikal kanser gelişmekte olan ülkelerde en sık görülen jinekolojik kanserdir (1). Hastaların sitolojik yöntem ve yüksek riskli Human Papilloma Virüsü (hrHPV) testi kullanarak düzenli olarak yapılan ulusal tarama programlarına dahil edilmesi ve servikal kanser öncül lezyonların tedavisi ile serviks kanserinin görülme sıklığı ve mortalitesi önemli ölçüde azaltılabilir (2). Çünkü serviks kanserinin ve servikal intraepitelyal neoplazilerin (CIN) gelişmesinde, yüksek riskli Human Papilloma virüsleri ile enfeksiyonlar en önde gelen risk faktörüdür (3,4). Günümüzde servikal kanser taraması için kullanılan testler; Pap testi, hrHPV testi veya hrHPV testi ve Pap testinin birlikte kullanıldığı (co-test) yöntemlerdir. Pap ve/veya hrHPV testi sonuçları anormal saptanan hastaların, altta yatan daha ciddi servikal lezyonun atlanmaması için kolposkopi ve servikal biyopsi ile detaylı değerlendirilmesi gerekmektedir. Ayrıca bu hastaların uzun dönem takibi çok önemlidir. Yüksek dereceli lezyonun dışlanamadığı atipik hücreler (ASC-H), önemi belirlenemeyen atipik skuamöz hücreler (ASC-US) ve yüksek dereceli intraepitelyal lezyon (HSIL) arasında kalan orta düzey ciddiyette sitolojik özelliklere sahiptir (2). ASC-H, yüksek dereceli skuamöz intraepitelyal lezyonunu (HSIL) işaret eden anlamlı sitolojik değişiklikleri içerir, fakat bu işaretler kesin HSIL tanısı için yeterli değildir (5). ASC-H, sitoloji raporlarında diğer servikal intraepitelyal neoplazilere (CIN) kıyasla daha nadir (%0.3) (6) rapor edilmesine rağmen, genellikle yüksek oranda HPV mevcudiyeti (7) ve alta yatan servikal intraepitelyal neoplaziler (CIN2, CIN3 CIS) veya invaziv kanser riski ile ilişkili olabilir (8). Bu nedenle uluslararası kılavuzlar servikal sitolojide ASC-H saptanan hastaların HPV test sonucundan bağımsız olarak doğrudan kolposkopiye yönlendirilmesini önermektedir (9). Yapılan çalışmalarda, ASC-H sitolojisi olan hastalarda, altta yatan yüksek dereceli lezyonlar çok çeşitli oranlarda saptandığından (10,11) bu hastalara en uygun yaklaşım konusunda sorular ortaya çıkmaktadır. Araştırmacılar, çeşitli klinik ve patolojik faktörlerin ASC-H yönetiminde faydalı olabileceğini önermektedir (12,13). Servikal sitolojisi ASC-H olan hastaların yönetim prosedürlerinin güvenliğini ve verimliliğini artırmak için CIN2 ve daha ciddi lezyonların (≥CIN2+) saptanmasında etkili olan faktörleri belirlemek önemli olabilir.

Biz bu çalışmamızda, servikal sitolojisi ASC-H olarak değerlendirilen kadınlarda altta yatan önemli patolojilerin prevalansını ve ≥CIN2+ lezyonlarla ilişkili risk faktörlerini değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEMLER

2014-2023 tarihleri arasında Akdeniz Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Cerrahisi Kliniğinde servikal sitoloji sonucu ASC-H olarak rapor edilen 98 hasta bu kesitsel çalışmaya dahil edildi. Çalışma Helsinki Deklarasyonu prensiplerine uygun olarak yapılmış ve çalışmaya katılan tüm hastalardan bilgilendirilmiş onam alınmıştır. Hastaların hepsine uluslararası kılavuzların önerdiği şekilde kolposkopi yapıldı. Araştırma etik kurul onayını (25.01.2024-TBAEK-66) aldıktan sonra hastaların klinik ve patolojik bilgileri retrospektif olarak medikal dosyalarından kaydedildi. Hastaların yaşı, başvuru şikayeti, vücut kitle indeksi, medeni durumu, menopoz durumu, doğum şekli, gebelik ve doğum sayısı, immünsüpresyon durumu, sigara kullanımı ve kontrasepsiyon yöntemi gibi karakteristik özellikleri, hrHPV test sonucu (pozitif/negatif), hrHPV tipi, kolposkopide saptanan transformasyon zon tipi, kolposkopik servikal biyopsi ve endoservikal kürtaj sonucu, servikal eksizyon işlem tipi (LEEP (Loop electrosurgical excision procedure)/ soğuk konizasyon), servikal eksizyon ve endoservikal küretaj patoloji sonucu, cerrahi sınır durumu, takip süresi, takiplerindeki tekrarlayan servikal eksizyon hikayesi kaydedildi. Gebe olan hastalar, daha önce serviks kanseri tanısı olanlar, diğer genital sistem kanseri ya da intraepitelyal neoplazi tanısı olanlar, daha önce anormal servikal sitoloji raporu olanlar, daha önce anormal servikal histolojiden dolayı servikal eksizyonel biyopsi yapılanlar, histerektomi geçirenler, pelvik radyoterapi alanlar ve medikal bilgilerine ulaşılamayan hastalar çalışma dışı bırakıldı.

Servikal tarama sıvı bazlı yöntem kullanılarak yapıldı. Standartlaştırılmış kolposkopik muayene ise Akdeniz Üniversitesi Tıp Fakültesi Hastanesi'nin kolposkopi ünitesinde deneyimli akademik personel tarafından gerçekleştirildi. Bütün kolposkopik bulgular Uluslararası Servikal Patoloji ve Kolposkopi Federasyonu'nun (IFCPC) 2011 yılı terminolojisine göre sınıflandırıldı (14). Transformasyon zon tipi, skuamo-kolumnar bileşkenin kolposkopik muayenede görünme oranlarına göre tip 1, 2 ve 3 olarak tanımlandı. Bütün hastalardan kolposkopik muayene sırasında saptanan anormal bulgulara göre servikal biyopsi ve endoservikal küretaj ile örnekler alındı. Tip 3 transformasyon zon tipine sahip hastalara endoservikal küretaj yapıldı. Tüm sitolojik ve patolojik örnekler hastanemizin patoloji bölümündeki jinekolojik patoloji konusunda deneyimli akademik çalışanlar tarafından değerlendirildi. Eksizyonel servikal işlemler, hastaların tedavi edildikleri yıllardaki ASCCP (American Society for Colposcopy and Cervical Pathology) kılavuzundaki önerilere uygun şekilde uygulandı. 24 yaşından genç hastalar, histopatolojik olarak kanıtlanmış CIN2 lezyon varlığında uluslararası kılavuzlara göre konservatif tedavilere yönlendirildi.

Hastalar kolposkopik biyopsi, endoservikal küretaj ve servikal eksizyonel biyopsi sonuçlarına göre ≤ CIN1 ve ≥CIN2 olarak iki gruba ayrıldı. ≤ CIN1 olarak sınıflandırılan grupta biyopsi sonuçları CIN1 (düşük dereceli servikal intraepitelyal neoplazi), kronik servisit, atrofi ve ekzoserviks yüzey epiteli, endoservikal polip

yer alırken, ≥CIN2 grubunda CIN2, CIN3, karsinoma in situ (CIS), adenokarsinoma in situ (AIS) ve invaziv kanser yer aldı. Hastaların takipleri 6 ayda bir kontrol sitoloji ile yapıldı.

İstatiksel analizler SPSS 27.0 for Windows programı (SPSS, Inc., Chicago, IL) kullanılarak yapıldı. Tanımlayıcı istatistikler için verilerin normal dağılımına bağlı olarak, ortalama (mean), standart sapma, medyan, minimum-maksimum değerler ve frekanslar kullanıldı. Veriler uygun olduğu yerlerde, ortalama ± standart sapma (SD), medyan ve n (%) olarak ifade edildi. Kategorik değişkenlerin karşılaştırılmasında Ki-kare testi kullanıldı.

Primer analizde ≥CIN2+ birincil hedef olarak kabul edildi. Tüm kohortun histopatolojik tanı analizi yapıldı. Ciddi servikal lezyonu işaret eden anlamlı prediktör değişkenleri belirlemek için binomial lojistik regresyon uygulandı. Kategorik prediktörler ve sonuç değişkeni arasında çapraz tablo (crosstab) oluşturuldu. Birincil son noktayla (≥CIN2+ lezyon) ilgisi olan tüm değişkenler tek değişkenli (univariate) olarak test edildi. p değerleri < 0,05 olan değişkenler çok değişkenli (multivariate) lojistik regresyon modeli için aday olarak kabul edildi. Çok değişkenli lojistik regresyon analizinde, p değerleri <0,05 istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya 98 hasta dahil edildi. Tablo 1'de hastaların demografik özellikleri gösterilmiştir. Hastaların ortalama yaşı 45,8±12,721 (22-71) olarak saptandı. Hastaların 21 tanesi (%21,4) nullipardı. Hastalardan sadece bir tanesinin Anti-HCV testi pozitif olarak rapor edildi, diğer hastaların Elisa testleri negatif idi. Kolposkopiden sonra hastaların %81,6'sına servikal ekziyonel işlem uygulandı. Hastalardan sadece iki tanesinde postoperatif dönemde kanama şikâyeti oldu ve sorunsuzca tedavi edildi. On iki hastaya takip sırasında ya cerrahi sınırlarda ≥CIN2 lezyonun devam etmesi ya da nüks sebebiyle re-LEEP işlemi uygulandı. Elli sekiz (%59,1) hastada ≤ CIN1 lezyon (düşük dereceli servikal intraepitelyal neoplazi, kronik servisit, atrofi, endoservikal polip ve ekzoserviks yüzey epiteli) saptanırken 40 (%40,8) hastada ≥CIN2 (CIN2, CIN3, karsinoma in situ (CIS), adenokarsinoma in situ (AIS) ve invaziv kanser) saptandı. Kolposkopik biyopsi ile servikal sitoloji sonucu ASC-H olan hastaların %65,7'sinde ≤ CIN1 lezyon saptanırken, ECC'de hastaların sadece %3'ünde CIN2 lezyon saptandı. Eksizyonel işlem uygulanan 80 hastanın %39,9'unda herhangi bir ≥CIN2 lezyonun var olduğu görüldü. Hiçbir hastada invaziv servikal kanser saptanmadı. (Tablo 2).

Servikal kanser gelişiminde rol alabilecek on üç tane klinik, obstetrik ve patolojik özellik tek değişkenli regresyon analizi ile değerlendirildi. Bu değişkenlerden sadece beş tanesi istatistiksel olarak anlamlı saptandı (p=0,05) (Tablo 1). Bu faktörler yaş<40 (p=0,003), hrHPV testi pozitifliği (p=0,001), VKİ <30 kg/m^2 (p=0.016), hastanın semptomatik olması (p=0.007) ve hastanın premenopozal (p=0.004) dönemde olması idi. Premenopozal dönem, hastanın yaşı ile korelasyon gösterdiğinden çok değişkenli analize dahil edilmedi. Çok değişkenli regresyon analizinde hastanın hrHPV test sonucu, kliniğe ilk başvuruda semptomatik olması, yaşı ve VKİ CIN2+ tanısı olasılığı üzerindeki etkisini değerlendirmek için analiz edildi. Semptomatik olan hastaların alt grup sayıları çok az olduğu için hastaların semptom tipine göre risk analizi yapılamadı. Hastaların HPV test sonuçlarına göre dağılımı incelendiğinde, 50 hastanın HPV negatif, 32 hastanın HPV pozitif ve 16 hastanın HPV test sonucunun bilinmediği saptandı. Tüm hastaların %36,7'sinin semptomatik, %32,6'sının 40 yaşından genç ve %90,8'nin VKİ'nin 30 kg/m^2'nin altında olduğu tespit edildi.

HPV test sonucu, semptom varlığı, yaş ve VKİ gibi değişkenler regresyon analizine dahil edildiğinde CIN2+ olmayan vakaların sınıflandırma doğruluğu %82,8, CIN2+ olan vakalarınki ise %72,5 olup, genel tahmin doğruluğu %78,6'dir. Çok değişkenli lojistik regresyon analizi, özellikle hrHPV testinin pozitif olmasının, CIN2+ sonuçlarının önemli bir öngörücüsü olduğunu ortaya koymaktadır; Exp(B) oranı 8,595 (95% confidence interval (CI); 2,871- 25,731) olup, hrHPV testinin pozitif saptandığı hastaların, HPV negatif bireylere göre CIN2+ tanısı alma olasılığının yaklaşık 8,6 kat daha yüksek olduğunu göstermektedir. Semptom varlığı da önemli bir öngörücü olup, semptomatik bireylerin CIN2+ sonuçlarına sahip olma olasılığının 3,355 kat (95% confidence interval (CI); 1,246-9,038) daha fazla olduğunu belirtmektedir. Ancak, yaş ve BMI bu modelde istatistiksel olarak anlamlı öngörücüler değildir (Tablo 3).

Regresyon analizinin uygunluğunu değerlendirmek için kullanılan Hosmer ve Lemeshow testi, 6 derece serbestlikle 5,582, χ^2 değeri (p=0,472) olarak hesaplanmış olup, bu da regresyon analizinin tahminlerinin gözlemlenen değerlerden önemli ölçüde farklı olmadığını ve dolayısıyla iyi bir uyum gösterdiğini açıklamaktadır.

TARTIŞMA

Biz bu çalışmada servikal sitoloji sonucu ASC-H olan hastalarda altta yatan ≥CIN2+ durumunu etkileyebilecek bir dizi faktör üzerine odaklandık ve bu faktörlerin etkilerini değerlendirmeye çalıştık. On üç tane değişkenin arasında yapılan regresyon analizinde sadece, hastanın semptomatik olması ve hrHPV test pozitifliği altta yatan ≥CIN2+ lezyonu öngörmede istatiksel olarak anlamlı saptanmıştır. hrHPV pozitif hastalarda ≥CIN2+ olma olasılığı negatif hastalara kıyasla 8,595 kat (95% confidence interval (CI); 2,871- 25,731) daha

Tablo 1. ≤ CIN1 ve ≥CIN2 olan hastaların demografik, klinik ve obstetrik özellikleri ve tek değişkenli regresyon analizi

	≤ CIN1 (n:58)	≥CIN2 (n:40)	p
Yaş, mean ± SD	48,9 +/- 12,7	41,3 +/- 11,4	**0,003**
VKİ (kg/m²), mean ± SD	28,3±5,8	24,1±5,7	**0,016**
Medeni durum, n (%)			
Bekar	13 (22,4)	13 (32,5)	0,266
Evli	45 (77,5)	27 (67,5)	
Parite, n (%)			
Nullipar	10 (17,2)	11 (27,5)	0.224
Multipar	48 (82,7)	29 (72,5)	
Gravida, mean± SD	2,47+/-1,77	2,05+/-1,65	0,237
Parite, mean± SD	1,78+/-1,14	1,6+/-1,2	0,482
Doğum şekli, n (%)			0,685
NSD	31 (53,4)	19 (47,5)	
C/S	10 (17,2)	6 (15)	
NSD+C/S	7 (12)	4 (10)	
Menopozal durum, n (%)			**0,008**
Premenopoz	28 (48,2)	30 (75)	
Postmenopoz	30 (51,7)	10 (25)	
Sigara, n (%)			0,219
İçiyor	15 (25,8)	15 (37,5)	
İçmiyor	43 (74,1)	25 (62,5)	
Kontrasepsiyon, n (%)			0,271
Kullanmıyor	41 (70,6)	25 (62,5)	
Kullanıyor	17 (29,3)	15 (37,5)	
Koitus interruptus	6 (10,3)	8(20)	
Kondom	7 (12)	2 (5)	
Sterilizasyon	1(1,7)	1(2,5)	
RİA	1(1,7)	1(2,5)	
OKS	2 (3,4)	3 (7,5)	
İlk şikâyet, n (%)			**0,007**
Asemptomatik	43 (74,1)	19 (47,5)	
Semptomatik	15 (25,8)	21 (52,5)	
Postkoital kanama	2 (3,4)	2 (5)	
Lökore	6 (10,3)	9 (22,5)	
Menometroraji	3 (5,1)	3 (7,5)	
Vajinal kaşıntı	0 (0)	3 (7,5)	
Genital siğil	0 (0)	3 (7,5)	
Diğer*	4 (6,8)	1 (2,5)	
İmmünosupresyon, n (%)			0,706
Var	18 (31)	11 (27,5)	
Yok	40 (68,9)	29 (72,5)	
Hpv durumu, n (%)			**0,001**
Pozitif	9 (15,5)	23 (57,5)	
Negatif	39(67,2)	11 (27,5)	
Bilinmiyor	10 (17,2)	6 (15)	
Transformasyon zonu tipi			0,14
Tip 1	23 (39,6)	24 (60)	
Tip 2	11 (18,9)	5 (12,5)	
Tip 3	24 (41,3)	11 (27,5)	

Not: *: pelvik ağrı, dismonere, inkontinans SD: standart sapma; VKİ: Vücut kitle indeksi; NSD: Normal spontan vajinal yolla doğum; C/S: Sezaryen seksiyo; RİA: Rahim içi araç; OKS: Oral kontraseptif ilaç HPV:Human papilloma virüs

Tablo 2. Hastaların kolposkopik muayene ve servikal işlem sonrasında saptanan histopatolojik bulgularının dağılımı

	Kolposkopik biyopsi n:91 (%)	Kolposkopik ECC n:97(%)	LEEP n:80(%)	LEEP ECC n:80 (%)
CİS	5 (5,4)	0	5 (6,2)	1 (1,2)
CIN3 (HSIL)	6 (6,5)	0	18 (22,5)	1 (1,2)
CIN2 (HSIL)	20 (21,9)	3 (3)	9 (11,2)	1 (1,2)
CIN1 (LSIL)	52 (57,1)	1 (1)	40 (50)	3 (3,7)
Kronik Servisit	5 (5,4)	11 (11,3)	5 (6,2)	3 (3,7)
Atrofi	0	0	2 (2,5)	-
Ekzoserviks yüzey epiteli	3 (3,2)	-	1 (1,2)	-
Endoserviks yüzey epiteli	-	76 (78,3)	-	71 (88,7)
Endoservikal polip	-	6 (6,1)	-	0

Not: CİS: karsinoma in situ; HSIL: Yüksek gradeli intraepitelyal neoplazi; LSIL: Düşük gradeli intraepitelyal neoplazi; CIN: Servikal intraepitelyal neoplazi ECC: Endoservikal küretaj LEEP: Loop Electrosurgical Excision Procedure

Tablo 3. ≥CIN2+ lezyon riskini artıran faktörlerin çok değişkenli lojistik regresyon analizi

	B	S.E	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
HPV durumu			16,170	2	,000			
hrHPV (+)	2,151	,559	14,786	1	,000	8,595	2,871	25,731
hrHPV (-)	,250	,762	,107	1	,743	1,284	,288	5,717
VKİ <30kg/m²	,125	,831	,023	1	,880	1,133	,222	5,783
Yaş <40	-,635	,612	1,077	1	,299	,530	,160	1,758
Semptomatik	1,211	,506	5,733	1	,017	3,355	1,246	9,038
Sabit	-1,219	,665	3,365	1	,067	,295		

Hosmer ve Lemeshow test değeri: 0.472

Nagelkerke R square test değeri: 0.343

Not: ≥CIN2+: Servikal intraepitelyal grade 2 ve üstü lezyon, hrHPV: Yüksek riskli Human Papilloma Virüs testi, VKİ: Vücut kitle indeksi, SE: Standard eror, df: degrees of freedom, CI: Confidence Interval

fazlaydı. Bu bulgu literatürdeki çalışmalarla da desteklenmektedir (13,15,16). Hastanın semptomatik olması ise altta yatan ≥CIN2+ lezyon ihtimalini 3,355 kat (95% confidence interval (CI); 1,246-9,038) artırmaktadır.

Çalışma popülasyonumuzun %59,1'inde ≤ CIN1 lezyon, %40,8'inde ise ≥CIN2 lezyon saptandı. CIN1 ve CIN2 için histolojik sonuçlarımız, CIN1 için %20,6 ila %69,8 ve CIN2 için %16,8 ila %52,0 aralığı bildiren diğer çalışmaların verileriyle benzerdi (10,15-17). HPV pozitif ve negatif ASC-H için anlık invaziv kanser oranları (%0.92 vs %0,69) (18) bildirilmesine rağmen biz hiçbir hastada invaziv servikal kanser saptamadık.

Sitolojisi ASC-H olan hastalarda yaş, menopoz durumu, transformasyon zon tipi ve VKİ gibi çeşitli klinik faktörlerin altta yatan ciddi lezyon riskini arttırdığı gözlemlenmiştir (13,16,19-21). Fakat biz çalışmamızda bu klinik faktörlerin altta yatan CIN2+ lezyonu öngörmede etkili olmadığını saptadık. Çalışmamızda transformasyon zon tipi ile CIN2+ lezyonu arasında herhangi bir ilişki kuramadık, fakat yakın zamanda yapılan çalışmalarda transformasyon tipi 3'ün CIN2+ lezyona karşı koruyucu olduğu gösterilmiştir (13,22). Tip 3 transformasyon zonunun daha çok postmenopozal kadınlarda görüldüğü ve bu hastalarda ASC-H sitolojisinin CIN2+ lezyondan daha çok mevcut atrofi ve östrojen eksikliği ile ilgili olduğu düşünüldüğünde, bu koruyucu etki mantığa yatkındır. Ayrıca yaşlı kadınlarda saptanan ASC-H sitolojisinin yanlış pozitiflik oranı atrofi nedeniyle daha yüksektir (23). Bu duruma benzer bir şekilde çalışmamızda çok değişkenli regresyon analizinde, yaş ile alta yatan CIN2+ lezyon arasında istatistiksel bir bağlantı kuramazken, çeşitli çalışmalar, ASCH hastalarında hastalığın sonuçlarında yaşın önemli bir faktör olduğunu belirlemiş ve genç kadınların CIN2+ lezyonları sergileme olasılığının yaşlı kadınlara göre daha yüksek olduğunu göstermiştir (24-27). Kaiser ve arkadaşlarının yaptıkları bir çalışmada ise bizim çalışmamıza benzer şekilde, yaş, CIN2+ lezyonu öngörmede etkili bir faktör olarak saptanmamıştır (13).

Tek değişkenli regresyon analizinde premenopozal durumun, postmenopozal duruma kıyasla CIN2+ lezyonu öngörmede daha etkili bir faktör olduğunu saptamamıza rağmen (p=0,008), premenopozal durumu, yaş ile çok yakından ilişkili olduğundan, çok değişkenli regresyon analizine dahil etmedik. Fakat bazı çalışmalarda

menopozal durumun izole ve etkili bir faktör olduğu gösterilmiştir (10,16,22). Menopozal durumun hasta yaşı ile bağlantısı çok kuvvetli olduğundan bu çalışmaların dikkatli değerlendirilmesi gerekir. Bizim analizlerimizin sonucuna göre genç, semptomatik ve hrHPV pozitif olan hastalarda, CIN2+ lezyon mevcut olma ihtimali, daha yaşlı, asemptomatik ve hrHPV testi negatif hastalara kıyasla daha fazla olduğundan bu hastalar kolposkopik muayene ile mutlaka değerlendirilmelidir. Bunun aksine postmenopozal dönemde hrHPV testi negatif ve rutin tarama sırasında ASC-H saptanan hastalar gereksiz işlemler uygulanmadan takip edilebilir. Bu klinik yaklaşım Cohen ve arkadaşlarının yaptıkları çalışmada da güvenli bir klinik uygulama olarak önerilmiştir (12). Bunun aksine hrHPV testi negatif olan ASC-H sitolojili postmenopozal kadınlar dikkatle takip edilmelidir, çünkü HPV testinin negatif olması alta yatan ciddi lezyon olmadığı göstermez. Ayrıca çalışmamızda kohortun küçük olmasından dolayı semptom tipine göre hangi hastaların CIN2+ lezyonu bakımından daha riskli olduğunu gösteremedik. Daha geniş popülasyon çalışmalarında belki bu konu açığa çıkarılabilir.

ASCCP 2019 kılavuzuna göre (bu tavsiyenin kanıt düzeyi orta olarak derecelendirilmesine rağmen) HPV sonucundan ve yaştan bağımsız sitoloji sonucu ASC-H için kolposkopi önerilmektedir. Yapılan çalışmalarda HPV pozitif ve negatif ASC-H için anlık CIN3 riski (%26 vs %3.4) farklılık göstermesine rağmen, benzer kanser oranlarına sahip olduğu gösterilmiştir (% 0.92 vs %0,69) (18). Bazı meta-analizler, ASC-H triajında hastalara HPV testinin yapılmasını ve sadece hrHPV testi pozitif hastalara kolposkopi önermektedir (2). Çünkü HPV testinin pozitif olmasının CIN2+ lezyonu tespit etmede yüksek doğruluk (%93) ve özgünlük (%45) oranına sahip olduğu gösterilmiştir (2).

hrHPV testinin ASC-H triajında yer almasını savunan araştırmalara ek olarak, bazı araştırmacılar, histolojik CIN2 ve CIN3'ü ön görmede bazı moleküler belirteçler üzerinde çalışmışlardır. Wang, ASC-H sitolojisinden sonra yüksek dereceli lezyonların tespitinde metilasyona duyarlı yüksek çözünürlüklü eritme (MS-HRM) ile eşleştirilmiş kutu gen 1 (PAX1) metilasyon analizinin rolünü araştırmış ve performansını Hybrid Capture 2 (HC2) insan papillomavirüs (HPV) testi ile karşılaştırmıştır. PAX1 MS-HRM testinin yüksek dereceli lezyonların tespitinde HR-HPV testine göre üstün olduğunu saptamıştır (duyarlılık 80.6% vs 67.7%, özgünlük 94.9% vs 54.5%, pozitif prediktif değer 83.3%, vs 31.8%, negatif prediktif değer 94.0% vs 84.4%, doğruluk 91.5% vs 57.7%) (28). $p16^{INK4a}$'nın hrHPV ile karşılaştırıldığı çalışmaların (29,30,31) derlendiği metaanalizde, $p16^{INK4a}$'nın hrHPV ile benzer duyarlılığa (%93, %95 CI:%75-100) sahip olduğu fakat özgüllüğünün daha iyi olduğu saptanmıştır (özgüllük oranı: 1,69) (2). hrHPV'yı kıyasla CIN2 ve daha üzeri lezyonları tespit etmede daha spesifik ve özgün başka belirteçler de tanımlanmıştır (32), fakat bu belirteçler günümüzde rutin pratikte kullanılmamaktadır. Bu nedenle bu çalışmada bu tür belirteçler araştırılmamıştır.

Çalışmamızın retrospektif tasarımından dolayı servikal kanser gelişiminde risk faktörü olan ilk koit yaşı, partner sayısı, cinsel yolla bulaşan hastalıkların varlığı, sosyoekonomik düzey, HPV aşısı ve geçmiş tarama (kotest) sonuçları gibi etkenleri araştıramadık. Hastaların kontrasepsiyon kullanma ya da kullanmama durumlarını regresyon analizinde değerlendirdik ve ≥CIN2+ lezyonla arasında herhangi bir ilişki bulamadık. Kontrasepsiyon yöntemlerinin ≥CIN2+ lezyon ile ilişkisi, çalışma popülasyonunun küçük olmasından dolayı analiz edilemedi. Aynı şekilde hastanın semptomatik olması altta yatan ≥CIN2+ lezyonu öngörmede değer taşırken çalışma popülasyonunun küçük olmasından dolayı hangi semptomun daha çok ≥CIN2+ lezyon ile ilişkili olduğu ortaya koyulamamıştır. Çalışma popülasyonumuzun küçük olması, ASC-H sitolojisinin nadir görülen bir sitoloji olmasından kaynaklanmaktadır.

SONUÇ

Sonuç olarak, bu çalışma, servikal sitolojisi ASC-H olan hastalarda, hrHPV testinin pozitif olması ve semptom varlığının CIN2+ varlığını öngörmede önemli faktörler olduğunu göstermektedir. Bu bulgular, özellikle HPV pozitif ve semptomatik bireyler arasında, CIN2+ risklerini etkin bir şekilde belirlemek ve yönetmek için artan bir farkındalık ve tarama çabalarının gerekliliğini öne sürmektedir.

Çıkar Çatışması

Herhangi bir çıkar çatışması bulunmamaktadır. Yazarlar tüm verilerin sorumluluğunu almaktadır ve istenildiği takdirde veriler gerekli kişiler tarafından incelenmek üzere verilebilir.

Teşekkür

Hastaların verilerinin dijital olarak kaydedilmesinde emeği geçen hastanemiz patoloji anabilim dalı ve arşiv çalışanlarına teşekkür ederiz.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Sarcomatous transformations causing early recurrence in malignant mixed germ cell tumor: from case to analysis

Malign miks germ hücreli tümörde erken nükse neden olan sarkomatöz dönüşümler: Vakadan analize

Zehra O. BASARIR[1], Mustafa SAHİN[2], Tufan ARSLANCA[1]

[1]Department of Gynecologic Oncology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Gynecologic Oncology, Konya City Hospital, Konya, Türkiye

ABSTRACT

Aim: Our aim is to analyze the malignant mixed germ cell tumors of the ovary that recur due to sarcomatous transformation in the literature, with a case report.

Materials and Methods: An electronic database search was conducted from January 1980 to January 2023 using PubMed/MEDLINE. We evaluated the 10 cases included in these articles together with our own case. Patient age (years), first surgery type, tumor types, adjuvant therapy type, recurrence time, recurrent tumor types, and recurrence site were analyzed.

Results: We evaluated 11 cases, including our own. The mean age of the 11 patients was 27.36±16.39 years. Nine patients (81.8%) had rhabdomyosarcoma differentiated areas in primary pathology. Ten patients (90.1%) received adjuvant chemotherapy. The mean recurrence time was 10±8.94 months, ranging from 2 to 24 months. Reported areas of recurrence included retroperitoneal, peritoneal, pelvic, scapula, aortic bifurcation, abdominal cavity, and mediastinal area.

Discussion: We compiled ten cases in the literature with rhabdomyosarcoma transformation, including our case. Although the prognosis of GCT depends on the clinical stage and location, the presence of a sarcomatous area in GCT is a factor indicating a more aggressive behavior. Diagnostic imaging, including PET-CT scans, can be used for staging recurrent lesions and demonstrating local lymphatic metastasis or lung metastasis, which may indicate sarcomatous differentiation.

Conclusion: In patients with sarcomatous differentiation, the choice of chemotherapy may vary according to this component. It is important to determine the presence of the sarcomatous component in malignant germ cell tumors with detailed pathological examination. Close follow-up with radiological means is crucial to detect early recurrence and distant metastases as a result of sarcomatous transformation, as in our case.

Keywords: Mixed germ cell tumors, ovarian mass during pregnancy, sarcomatous transformation

ÖZ

Amaç: Amacımız literatürde sarkomatöz transformasyona bağlı olarak tekrarlayan overin malign mikst germ hücreli tümörlerini bir olgu sunumu eşliğinde incelemektir.

Gereç ve Yöntemler: PubMed/MEDLINE kullanılarak Ocak 1980'den Ocak 2023'e kadar elektronik veri tabanı araştırması yapıldı. Bu yazılarda yer alan 10 olguyu kendi olgumuzla birlikte değerlendirdik. Hasta yaşı (yıl), ilk ameliyat tipi, tümör tipleri, adjuvan tedavi tipi, nüks zamanı, nüks tümör tipleri ve nüks bölgesi analiz edildi.

Bulgular: Kendi vakamız da dahil 11 vakayı değerlendirdik. 11 hastanın yaş ortalaması 27,36±16,39 yıldı. Dokuz hastada (%81,8) primer patolojide rabdomiyosarkomun farklılaştığı alanlar vardı. On hasta (%90,1) adjuvan kemoterapi aldı. Ortalama nüks süresi 10±8,94 ay olup 2 ile 24 ay arasında değişmektedir. Bildirilen nüks alanları arasında retroperitoneal, peritoneal, pelvik, skapula, aort bifürkasyonu, karın boşluğu ve mediastinal alan yer alıyordu.

Tartışma: Literatürde rabdomiyosarkom dönüşümü olan 10 olguyu, bizim olgumuz da dahil olmak üzere derledik. GCT'nin prognozu klinik evreye ve lokasyona bağlı olmakla birlikte, GCT'de sarkomatöz alanın varlığı daha agresif davranışı gösteren bir faktördür. PET-CT taramaları da dahil olmak üzere tanısal görüntüleme, tekrarlayan lezyonları evrelemek ve sarkomatöz farklılaşmayı gösterebilecek lokal lenfatik metastazı veya akciğer metastazını göstermek için kullanılabilir.

Sonuç: Sarkomatöz farklılaşma olan hastalarda kemoterapi seçimi bu bileşene göre değişiklik gösterebilmektedir. Malign germ hücreli tümörlerde sarkomatöz bileşenin varlığının ayrıntılı patolojik inceleme ile belirlenmesi önemlidir. Bizim olgumuzda olduğu gibi sarkomatöz dönüşüm sonucu ortaya çıkan nükslerin ve uzak metastazların erken tespiti açısından radyolojik yöntemlerle yakın takip çok önemlidir.

Anahtar Kelimeler: Mikst germ hücreli tümörler, gebelikte over kitlesi, sarkomatöz transformasyon

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Sorumlu Yazar/Corresponding Author: Mustafa SAHIN, Department of Gynecologic Oncology, Konya City Hospital, Konya, Türkiye
E-mail: bmustafasahin1163@gmail.com

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INTRODUCTION

Malignant ovarian germ cell tumors (OGCTs) are rare ovarian cancers that comprise less than 5% of all ovarian tumors (1,2). The mixed form of malignant OGCT includes more than one pathological component, most commonly combinations of dysgerminoma, endodermal sinus tumor, and immature teratoma (3). In contrast with more common epithelial ovarian cancers, they usually occur in younger women of childbearing age, grow rapidly, and therefore become symptomatic earlier (4). They may also occur during pregnancy, which may cause obstetrical complications (2,5). These tumors are usually chemosensitive, and prompt diagnosis with multimodal management may improve both prognosis and fertility (4,5).

Mixed malignant OGCTs may undergo sarcomatous transformation extremely rarely. This transformation can alter the oncological behavior, potentially causing recurrences and negatively affecting prognosis (6,7,8). These tumors have a variable prognosis depending on the type of sarcomatous differentiation and stage. Sarcomatous areas may cause early metastasis, indicating a poor prognosis. Early diagnosis, prompt treatment, and close follow-up of early metastasis play a critical role in management. We aimed to present our case as a very rare example of sarcomatous differentiation into rhabdomyosarcoma in a mixed malignant germ cell tumor of the ovary and to review the literature.

MATERIALS AND METHODS

Ethics committee approval was received from Ankara Bilkent City Hospital Medical research scientific and ethical review board for this study (TABED 1-25-961). Written informed consent was obtained from the patient for publication of this case report and accompanying images. Data regarding the patients were obtained from our hospital's electronic database system and patient files.

Literature Review: A systematic review of the medical literature was performed to identify articles. An electronic database search was conducted from January 1980 to January 2024 using PubMed/MEDLINE. The search terms included "Malignant Mixed Germ Cell Tumor", "Sarcomatous Transformation", "adnexal mass", "lung cancer", "ovarian cancer", "medical subject headings" (MeSH), or "keywords". At the end of the search, 10 articles were eligible for further analysis. We evaluated the 11 cases included in these articles together with our own case. Patient age (years), first surgery type, tumor types, adjuvant therapy type, recurrence time, recurrent tumor types, and recurrence site were analyzed.

Case Presentation: A 20-year-old primigravid woman was referred to our center after detection of a 150x100 mm heterogeneous mass during an ultrasonographic control of her 34-week, 3-day pregnancy. She had no history of myoma or adnexal mass prior to pregnancy. Tumor markers were cancer antigen 125 (CA125): 50 U/mL, CA19.9: 33 U/mL, CA15.3: 33 U/mL, carcinoembryonic antigen (CEA): <0.5 ng/mL, Alpha-fetoprotein (AFP): 5448.5 µg/L.

A detailed transabdominal ultrasound was performed and showed a single fetus and a 100x104x117 mm heterogeneous mass located in the lower segment of the uterus, filling the Douglas pouch. Magnetic resonance imaging (MRI) on T1-weighted images showed the lesion was multilocular cystic in nature, compressing the cervix anteriorly and the rectosigmoid colon posteriorly (Figure 1).

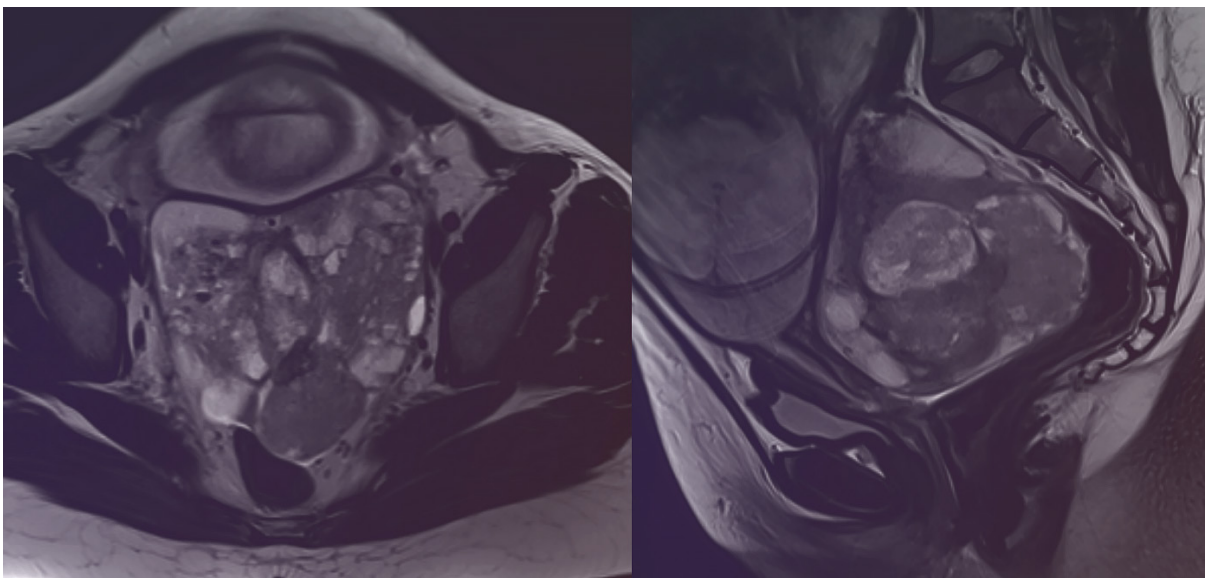
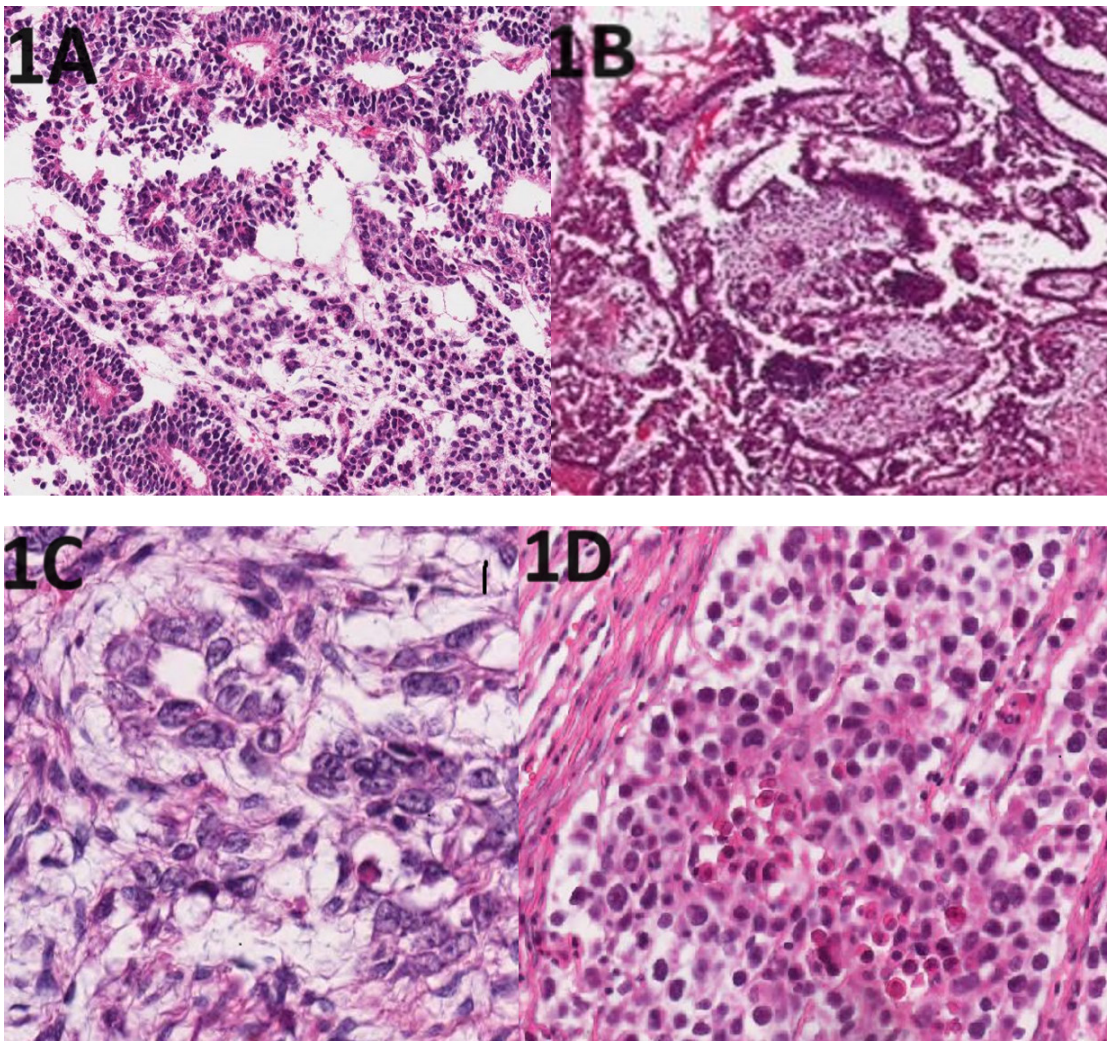


Figure 1. Non-contrast pelvic diffusion magnetic resonance imaging (MRI) on T1-weighed images, the lesion was multilocular cystic nature, and compressing the cervix anteriorly and the rectosigmoid colon posteriorly.

She underwent cesarean section at term and subsequent abdominal cytology. Mass resection and unilateral salpingo-oophorectomy were performed. There were no palpable lymph nodes in the pelvic and paraaortic areas. The appendix was microscopically normal. No implants were found on the surface of the diaphragm, bladder, or mesothelium of the colon and intestine. Frozen sections were reported as immature cystic teratoma, and multiple biopsies were taken from the omentum and peritoneum. Pathologically, the mass was diagnosed as a mixed malignant germ cell tumor of the ovary. Macroscopically, the left ovary measured 25×27×8 cm and weighed 3980 grams. Microscopically, the tumor was composed of 65% mature teratoma, 15% embryonal carcinoma, 10% yolk sac tumor, and 10% dysgerminoma. Immunohistochemical studies showed diffuse positivity for OCT3/4 and D2-40 in dysgerminoma areas, focal staining for AFP in yolk sac tumor areas, and OCT3/4 in embryonal carcinoma areas. Trophoblastic cells within embryonal carcinoma were stained for B-HCG. CD-34 was positive in vessel walls and some components of teratoma. CD30 and glypican-3 couldn't be evaluated for technical reasons (Images 1A, 1B, 1C, 1D).

The patient then received chemotherapy consisting of 3 cycles of BEP (bleomycin, etoposide, and cisplatin).

Radiological examination after three months of additional chemotherapy demonstrated disease progression as increased size of pelvic mass on abdominal CT up to 87x75x80 mm, increased number of pelvic lymph nodes, increased FDG uptake on PET scan (SUV max 18.95), and a newly formed 36x20 mm anterior mediastinal mass (Figure 2). Blood tests were total hCG: <2 mIU/mL, CEA: 1.2 ng/mL, CA 125: 31 U/mL, CA15.3: 15 U/mL, CA19.9: <1.3 U/mL, AFP: <1.3 µg/L.



Images 1. 1A. Photomicrograph (Haemotoxyline and Eosin, original magnification ×200) of immature teratoma shows presence surrounding primitive mesenchyme. **1B**. Yolk sac tumor tissue immunohistochemically positive for alpha fetoprotein. **1C**. Embryonal carcinoma component (large pleomorphic cells with cytologic atypia). **1D**. Dysgerminoma component in tumor tissues (Centrally located, round to oval nuclei, often with angulated, squared off borders with granular or coarse chromatin).

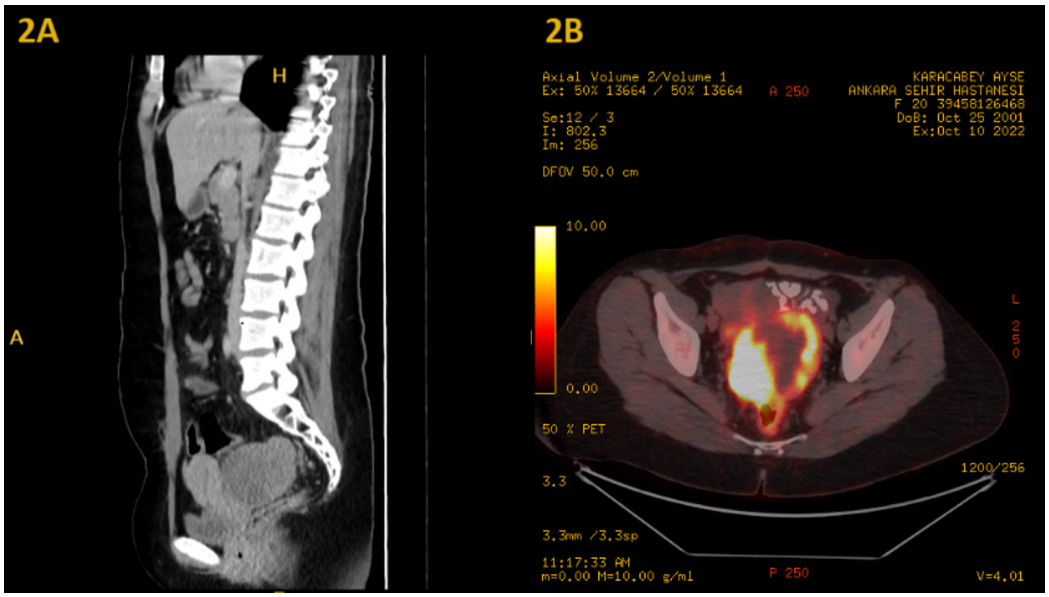
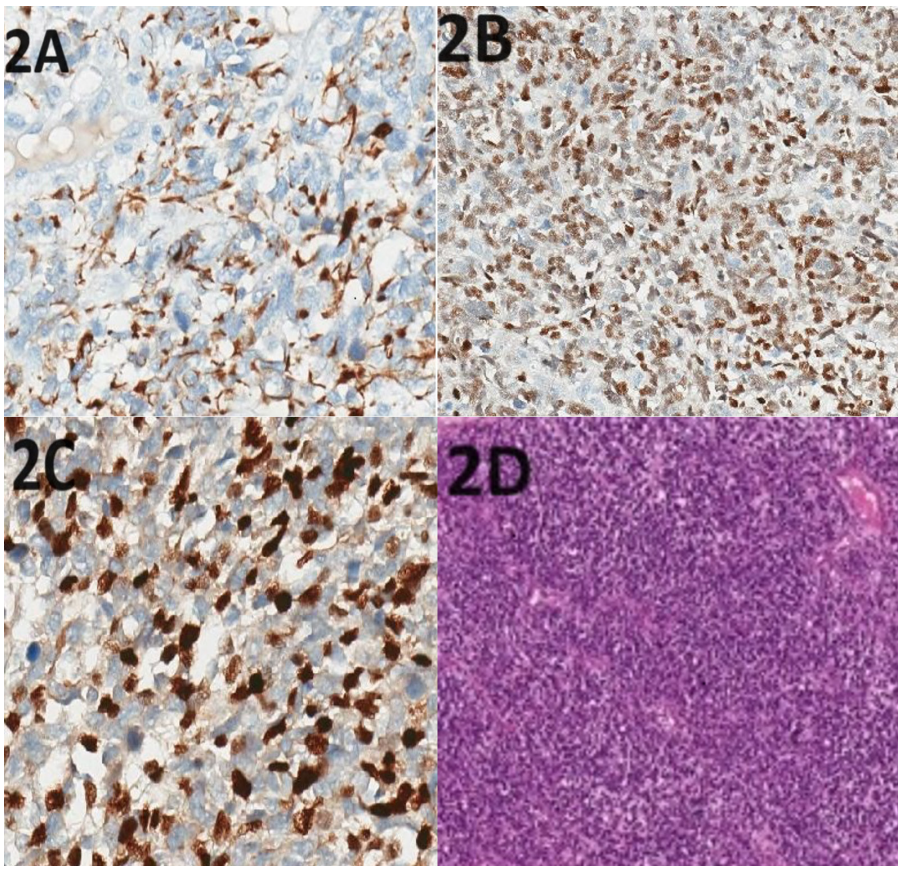


Figure 2. Postcontrast abdominal CT and PET images of pelvic recurrens after 3 months. 2A. Abdominal CT: As size of recurrence pelvic mass up to 87x75x80 mm, increased number of pelvic lymph nodes. 2B. PET scan: İncreased FDG uptake on (SUV max 18.95) and newly formed 36x20 mm anterior mediastinal mass.

She underwent second-look laparotomy (SLL). A solid fixed mass of 90x75x85 mm was detected in the left adnexal region. Along with excision of the mass, total abdominal hysterectomy, right unilateral salpingo-oophorectomy, low rectal anastomosis, total omentectomy, and pelvic and para-aortic lymph node dissection were performed. Frozen analysis was reported as malignant germ cell tumor.

Detailed pathological examination revealed rhabdomyosarcoma (RMS) metastasis with reactive lymph nodes. Immunohistochemical staining showed myoD1, myogenin, desmin, WT1, vimentin, p16, and CD56 positivity in tumor tissue (Images 2A, 2B, 2C, 2D). The tumor was negative for SMA, calretinin, GFAP, CD117, LCA, HMB45, MelanA, CK8/18, panCK, EMA, DOG1, CD34, betaHCG, glypican, OCT3/4, CK7, CK20, CD30, AFP, D2-40, PAX8, CD99, chromogranin, and synaptophysin.



Images 2. 2A. Desmin positivity in tumor cells. **2B**. myoD1 positivity in tumor cells. **2C**. Myogenin positivity in tumor cells. **2D**. Abundant acidophilic cytoplasm with small pleomorphic spindle cells with hyperchromatic nuclei in slightly myxoid matrix (H&E X40) Rhabdomyosarcoma differentiation.

Table 1. Sarcomatous transformation in ovarian germ cell tumors

Ref. no	Case	Age	First surgery	Tumor types	Adjuvant therapy	Recurrence time	Recurrent tumor	Recurrence site
13.	Malagon et al.	25	Oophorectomy	MT, IT, ***RMS***	Chemotherapy	24 months	RMS	Retroperitoneal
13.	Malagon et al.	25	Oophorectomy	MT, IT, D, ***RMS***	Chemotherapy	21 months	IT, RMS	Peritoneal
14.	Yanai et al.	6	Oophorectomy	IT, ***RMS***	VAC	10 months	RMS	Pelvic
15.	Ergeneli et al.	44	Staging	MCT, ***RMS***	CI	2 months	RMS	Scapula
16.	Kabukcuoglu et al.	23	Right SO	IT, D, YS, ***RMS***	VAC	NR	NR	FR
17.	Amada et al.	33	BSO	IT	VAC	5 months	RMS	Aortic bifurcation
18.	Al-Jumaily et al.	12	Right SO	MCT, ***RMS***, YS, EC, CC	BEP, VAC	NR	None	DFS (36 months)
19.	Kefeli et al.	65	BSO, omentectomy	MCT, ***RMS***, SC	Platinum based	NR	None	Follow-up 3 months
20.	Haj Salah et al.	15	Left cystectomy	IT, YS, ***RMS***	NR	NR	NR	NR
21.	Kawaı et al.	33	Right SO	IT, ***RMS***	FAMT	5 months	RMS	Abdominal cavity
	Present case	20	Left SO	MCT, EC, YC, D	BEP	3 months	RMS	Pelvic, mediastinal

SO:Salpingoopherectomy; BSO: Bilateral salpingoophorectomy; MCT:Mature cystic teratoma; EC:Embryonal carcinoma; YS:Yolk sac; D:Dysgerminoma; IT: Immature teratoma; RMS:Rhabdomyosarcoma; SC:Squmaous carcinoma; CC: Choriocarcinoma; BEP: Bleomycin, Etoposide, Cisplatin; VAC:Vincristine, Actinomycin, Cyclophosphamide; FAMT: 5-Fluorouracil (5 FU) Cyclophosphamide, Mitomycin C, Chromomycin A; CI: Cisplatin, Ifosfamide; FR: Follow Refuse; DFS: Disease Free Survive; NR: Not reported

She was referred to medical oncology for further chemotherapy. She received 4 cycles of vincristine, actinomycin, and cyclophosphamide. At the latest follow-up at 24 months, she had no evidence of disease on PET-CT scan and abdominal ultrasound.

RESULTS

The pathologies of a total of 10 patients in the literature were evaluated. We assessed 11 cases, including our own case (Table 1). The mean age of the 11 patients was 27.36±16.39 years, with ages ranging between 6 and 65 years. Cystectomy, oophorectomy, salpingo-oophorectomy, and staging surgery were performed on the patients. Nine patients (81.8%) had rhabdomyosarcoma differentiated areas in primary pathology. Two patients (18.2%) did not have rhabdomyosarcoma differentiated areas in primary pathology. Ten patients (90.1%) received adjuvant chemotherapy, while one patient's adjuvant therapy status was not reported. The mean recurrence time was 10±8.94 years, ranging from 2 to 24 years. Reported areas of recurrence included retroperitoneal, peritoneal, pelvic, scapula, aortic bifurcation, abdominal cavity, and mediastinal area.

DISCUSSION

Malignant germ cell tumors are usually seen in the reproductive period, and their coexistence with pregnancy is more common (5). The rapid growth tendency of these lesions usually results in large masses that become symptomatic at an earlier stage, as seen in our patient. Mixed morphology is rarely observed (<1%), and the combination of histological subtypes determines the clinical behavior (9). Normal fetal outcome and long-term survival of the patient are the main goals of the treatment plan, which includes fertility-sparing surgery and adjuvant chemotherapy.

Diagnosis in the presence of mixed morphology is not straightforward due to the presence of various cell types. Immunochemistry usually contributes to the correct diagnosis, together with serum markers whenever possible (10). Histologically, dysgerminoma and endodermal sinus tumor are the most common subtypes of malignant mixed germ cell tumors (9,11). In our patient, dysgerminoma was accompanied by mature teratoma, embryonal carcinoma, and yolk sac tumor. Combined chemotherapy and surgery may achieve survival rates above 90% and protect reproductive potential (5,12,13). Our patient underwent conservative surgery (USO) together with chemotherapy, as in most of the reported cases (13-15). Surgical staging in our patient was performed due to the ongoing pregnancy, and all tissue biopsies obtained from the omentum and adjacent tissues were negative.

These heterogeneous tumors have the capacity to progress to higher or lower grades of differentiation, and sarcomatous differentiation of pathological subcomponents may result in a more aggressive clinical course with early recurrence and distant metastasis (3,16). Laboratory tests may be silent at the time of recurrence due to the

undifferentiated nature of RMS (13,21). Most of the reported cases had sarcomatous differentiation in their recurrent lesions, as seen in our case (Table 1). There were six recurrences in ten reported patients with RMS and mixed malignant germ cell tumors (13-18). In five of them, sarcomatous areas were detected in primary resection (13-16,21). Only Amada et al. reported a recurrent RMS without a sarcomatous nidus, similar to our patient. Early recurrence within six months was also similar to our patient (four months) (17). Normal levels of serum markers in our patient were also accepted as an indication of malignant transformation. Diagnostic imaging, including PET-CT scans, can be used for staging recurrent lesions and demonstrating local lymphatic metastasis or lung metastasis, which may indicate sarcomatous differentiation, as seen in our case.

Although conservative treatment with preservation of fertility may be achieved in ovarian malignant mixed germ cell tumors, more aggressive surgery and chemotherapy adapted to the new sarcoma diagnosis are vital elements of disease management after transformation (5,22-23). We suggest that close radiological follow-up, in the presence of normal blood tests, and a new chemotherapy regimen considering the RMS component, were responsible for the disease control obtained for more than two years despite early recurrence.

Our case demonstrates both the difficulties of obtaining the correct diagnosis and treatment of malignancy during pregnancy and the necessity for close follow-up in mixed malignant germ cell tumors of the ovary.

CONCLUSION

Although the prognosis of GCT depends on the clinical stage and location, the presence of a sarcomatous area in GCT is a factor indicating a more aggressive behavior. In patients with sarcomatous differentiation, the choice of chemotherapy may vary according to this component. It is important to determine the presence of the sarcomatous component in malignant germ cell tumors with detailed pathological examination. Additionally, close follow-up with radiological means is crucial to detect early recurrence and distant metastases as a result of sarcomatous transformation, as in our case.

Conflict of Interest
The authors have no conflicts of interest to disclose.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Comparison of Grade 3 endometrioid type endometrial cancer with clear cell and serous type endometrial cancer in terms of clinicopathology and survival, and examination of prognostic factors affecting survival

Grade 3 endometrioid tip endometrium kanseri ile berrak hücreli ve seröz tip endometrium kanserlerinin klinikopatolojik ve sağ kalım açısından karşılaştırılması ve sağ kalımı etkileyen prognostik faktörlerin incelenmesi

Fatma Nazlı DEMİR[1], Özgün CEYLAN[2], Zeliha FIRAT CÜYLAN[3], Bülent ÖZDAL[3]

[1]Kastamonu Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum, Kastamonu, Türkiye
[2]Etlik Şehir Hastanesi, Jinekolojik Onkoloji Cerrahisi, Ankara, Türkiye
[3]Ankara Şehir Hastanesi, Jinekolojik Onkoloji Cerrahisi, Ankara, Türkiye

ABSTRACT

Aim: Comparison of the similarities of grade 3 endometrioid type endometrial cancer with clear cell and serous type endometrial cancer in terms of clinicopathology and survival and examination of prognostic factors affecting survival.

Materials and Methods: The medical records of 207 patients who were diagnosed with clear cell, serous and grade 3 endometrioid type endometrial cancer and who underwent surgery at Zekai Tahir Burak Women's Health Training and Research Hospital between June 2007 and September 2019 and at Ankara City Hospital between September 2019 and April 2022 were reviewed and their demographic, surgical and pathological features were analyzed. The patients were divided into two groups as grade 3 endometrioid type endometrial cancer and serous/clear cell endometrial cancer, and the patients were compared in terms of clinical and demographic features with univariate-multivariate analyses.

Results: The mean age of the patients was 63.3±9.3 years. The rate of early stage disease in the grade 3 endometrioid group was significantly higher (66.3%-44.9%, p=0.002). In the grade 3 endometrioid group, adnexal invasion rate (13.5%-31.4%, p=0.003), uterine serosal invasion rate (10.1%-22%, p=0.023), positive cytology rate (10.1%-29.7%, p=0.001), lymph node metastasis rate (20.2%-43.2%, p=0.001) and abdominal metastasis rate (9%-28%, p=0.001) were significantly lower than in the serous/clear cell group. There was no significant difference between the two groups in terms of overall survival times of 12-18-24-36 months (p=0.910). According to the univariate analysis between the groups, there was a significant risk for overall survival in age categories (p=0.039) and stages (p=0.034). In the multivariate analysis, age over 63 and advanced stage disease were evaluated as poor prognostic factors.

Conclusion: There was no significant difference in survival between grade 3 endometrial cancer and serous and clear cell endometrial cancers. Being over 63 years of age and having advanced-stage disease were considered poor prognostic factors.

Keywords: Endometrioid, serous, clear cell

ÖZ

Amaç: Grade 3 endometrioid tip endometrium kanseri ile berrak hücreli ve seröz tip endometrium kanserinin klinikopatolojik ve sağkalım açısından benzerliğinin karşılaştırılması ve sağ kalımı etkileyen prognostik faktörlerin incelenmesi.

Gereç ve Yöntemler: Haziran 2007 ile eylül 2019 yılları arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi ile Eylül 2019 ile Nisan 2022 yılları arasında Ankara Şehir Hastanesi'nde ameliyat olup berrak hücreli, seröz ve grade 3 endometrioid tip endometrium kanseri tanısı almış 207 adet hastanın medikal kayıtları incelenerek demografik, cerrahi ve patolojik özellikleri analiz edildi. Hastalar grade 3 endometriod tip endometrium kanseri ve seröz/berrak hücreli endometrium kanseri olarak iki gruba ayrıldı ve hastalar klinik ve demografik özellikler yönünden univaryan-multivaryan analizlerle karşılaştırıldı.

Bulgular: Hastaların yaş ortalaması 63.3±9.3 idi. Grade 3 endometrioid grubun erken evre olma oranı anlamlı şekilde daha yüksekti (%66.3-%44.9, p=0,002). Grade 3 Endometrioid grubunda, seröz/berrak hücreli gruba göre adneksal invazyon oranı (%13.5-%31.4, p=0,003), uterin serozal invazyon oranı (%10.1-%22, p=0,023), pozitif sitoloji oranı (%10.1-%29.7, p=0,001), lenf nodu metastazı oranı (%20.2-%43.2, p=0,001) ve abdominal metastaz oranı (%9-%28, p=0,001) anlamlı olarak daha düşüktü. Her iki grup arasında 12-18-24-36 aylık genel sağkalım süreleri açısından anlamlı fark yoktu (p=0,910). Gruplar arasında yapılan tek değişkenli analize göre yaş kategorilerinde (p=0,039) ve evreler arasında (p=0,034) genel sağkalım için anlamlı bir risk vardı. Multivariant analizde yaşın 63'ün üzerinde olması ve ileri evre hastalık kötü prognostik faktör olarak değerlendirildi.

Sonuç: Grade 3 endometrium kanseri ile seröz ve berrak hücreli endometrium kanserleri arasında sağkalım açısından anlamlı bir fark yoktu. 63 yaş üzeri olmak ve ileri evre hastalığa sahip olmak kötü prognostik faktör olarak değerlendirildi.

Anahtar Kelimeler: Endometrioid, seröz, berrak hücreli

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Sorumlu Yazar/Corresponding Author: Özgün CEYLAN, Etlik Şehir Hastanesi, Jinekolojik Onkoloji Cerrahisi, Ankara, Türkiye
E-mail: ozguncyln@hotmail.com

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INTRODUCTION

Endometrial carcinoma (EC) is the second most common gynecological malignancy worldwide, considering both developed and resource-limited countries (1). The incidence of EC is increasing due to several factors, including increasing life expectancy, prevalence of obesity, and changes in reproductive behavior (eg, increasing prevalence of nulliparity). Available data suggest that the presence of early symptoms, such as metrorrhagia or postmenopausal bleeding, allows approximately 67% of patients diagnosed with EC to be diagnosed at an early stage when the disease is confined to the uterus (2).

The histological type of the tumor is an important prognostic factor in EC. In the classification of uterine corpus tumors published in 2020, the World Health Organization (WHO) defined the histological subgroups of EC's as follows: endometrioid carcinoma, serous carcinoma, clear cell carcinoma, mixed carcinoma, undifferentiated/dedifferentiated carcinoma, carcinosarcoma and rare EC subtypes (3). Endometrioid carcinoma (EEC) is the most common EC histology, accounting for 75 to 80 percent of cases. This is followed by serous carcinoma (SEC) at approximately 10% and clear cell carcinoma (CCEC) at <5%. The International Federation of Gynecology and Obstetrics (FIGO) 2023 staging system also divides EC into two categories: aggressive and non-aggressive tumors (4). Histopathological findings were centralized in the renewed FIGO staging system. In this revised staging, non-aggressive histological types are composed of low-grade EEC (grade 1 and 2), while aggressive histological types are composed of high-grade EEC (grade 3), SEC, CCEC, undifferentiated carcinoma, carcinosarcoma, and mesonephric-like and gastro-intestinal type mucinous carcinomas. Aggressive histological types have a higher incidence of extrauterine disease at presentation(5).

Histological grade is another factor that determines the prognosis, especially in EEC (6). EECs are graded using the FIGO classification system, which primarily based on architectural features. Low-grade EECs are defined into grade 1 and 2 tumors, which exhibit up to 5% and 6%–50% solid non-glandular growth, respectively. On the other hand, high-grade EECs (grade 3) are characterized by 50% or more solid component (7). These two categories differ in incidence and clinical behavior and affect postoperative adjuvant therapy. The aim of this study is to compare grade 3 EEC with SEC and CCEC in terms of clinicopathology and survival.

MATERIALS AND METHODS

We included 207 patients with clear cell, serous and grade 3 endometrioid type endometrial cancer diagnosed at Zekai Tahir Burak Women's Health Training and Research Hospital between June 2007 and September 2019 and Ankara City Hospital between September 2019 and April 2022. Medical and pathology reports of the patients were retrospectively analyzed. Patients who received neoadjuvant treatment, patients with incomplete medical information, patients diagnosed with secondary primary endometrial cancer were not included in the study. Ethics committee approval for our study was received from Ankara City Hospital Ethics Committee No. 2. (Number: E. Committee- E2-22-2080). All patients' consent that their medical information could be used in academic studies was obtained during the application process to the hospital, and the study was conducted in accordance with the Declaration of Helsinki.

All 207 patients included in the study underwent total hysterectomy + bilateral salpingoophorectomy (TAH + BSO) ± pelvic and/or paraaortic lymphadenectomy (PLND and/or PPLND) with laparoscopy or laparotomy procedure in primary surgical treatment. All materials were evaluated by gyneco-oncologic pathologists in the pathology department of our hospital. FIGO 2009 surgical staging and FIGO 1988 grading system were used for endometrial cancer staging. Cases treated before 2009 were restaged according to the FIGO 2009 staging system. Pelvic lymph node dissection was defined as excision of external iliac, internal iliac, common iliac and obturator lymph nodes, while paraaortic lymph node dissection was defined as excision of lymph nodes above the inferior vena cava and aorta up to the level of the renal vein. Blood samples for the analysis of cancer antigen-125 (CA-125) levels were obtained from the patients during the preparation for surgery.

Demographic, clinical, surgical and pathological characteristics were determined and analyzed from the patients medical records. Grade, tumor size, depth of myometrial invasion (MI), lymph node (LN) metastasis (pelvic, paraaortic), cervical involvement, adnexal metastasis, uterine serosal involvement, cytology and lymphovascular space invasion (LVSI) were evaluated. SEC/CCEC and grade 3 EEC were divided into two groups and compared by univariate-multivariate analyses in terms of clinical and demographic characteristics such as age, CA-125, stage, surgery performed, tumor size, depth of MI, cervical involvement, adnexal metastasis, uterine serosal involvement, cytology and LVSI.

Statistical analysis

The analyses were evaluated in SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 package program. Descriptive data were presented as n and % values for categorical data, mean±standard deviation (Mean±SD) and median (minimum-maximum) values for continuous data. Chi-square analysis (Pearson chi-square) was used to compare categorical variables between

groups. The compatibility of continuous variables with normal distribution was evaluated by Kolmogorov-Smirnov test. Student's t-test was used for normally distributed variables and Mann Whitney U-test was used for non-normally distributed variables. Overall and progression-free survival were evaluated by Kaplan-Meier for univariate analysis. Log rank (Mantel-Cox) analysis was used to compare survival time between categorical variables. For multivariate analysis of local control, Cox regression including all factors in the univariate analysis was performed. Statistical significance level was accepted as $p<0.05$ in the analyses.

RESULTS

A total of 207 patients were included in the study, 89 (43%) of whom were grade 3 EEC and 118 (57%) were SEC/CCEC. The mean age of grade 3 EEC patients was 63.6±9.6 years and the mean age of SEC/CCEC patients was 63.2±9.2 years and there was no statistically significant difference between them (p=0.786). The median CA-125 value of the patients was calculated as 16.0 IU/ml (range, 2.0-5536). While 146 (74.5%) of the patients had a CA-125 value of 35 IU/ml and below, 50 (25.5%) had a CA-125 value of 35 IU/ml and above. There was no significant difference between the groups in terms of CA-125 (p=0.059).

Total abdominal hysterectomy and bilateral salpingoopherectomy + cytology was performed in 4 (1.9%) patients, TAH + BSO + cytology + PLND in 5 (2.4%) patients, and TAH + BSO + cytology + PPLND in 198 (95.6%) patients. The median tumor size was 4.0 cm (range, 0.1-20.0). Cervical involvement was seen in 62 (30%), adnexal involvement in 49 (23.7%), uterine serosal involvement in 35 (16.9%), and LVSI in 125 (60.4%) patients. The depth of MI was <50% in 87 (42%) patients and 50% or more in 120 (58%) patients. Lymph node metastases were seen in 69 (33.3%) patients, 22 (10.6%) had isolated pelvic LN, 12 (5.8%) had isolated paraaortic LN and 41 (19.8%) had abdominal metastases. According to the 2009 FIGO staging system, in the grade 3 EEC, stage IA was seen in 28.1%, stage IB in 28.1%, stage II in 10.1%, stage IIIA in 6.7%, stage IIIB in 1.1%, stage IIIC in 18% and stage IV in 7.9%. On the other hand, 22% of the patients in the SEC/CCEC group had stage IA, 16.1% had stage IB, 6.8% had stage II, 0.8% had stage IIIB, 28.8% had stage IIIC and 25.4% had stage IV and there was a significant difference between the groups in terms of stage (p<0.001). The early stage rate of the grade 3 EEC group (66.3%) was significantly higher than the early stage rate of the SEC/CCEC group (44.9%) (p=0.002). The tumor size of the grade 3 EEC group was significantly higher than the tumor size of the SEC/CCEC group (p=0.001).

Comparison of clinical features of patients according to groups is shown in Table 1. The rate of adnexal invasion (13.5%-31.4%, p=0.003), uterine serosal invasion (10.1%-22%, p=0.023), positive cytology (10.1%-29.7%, p=0.001), LN metastasis (20.2%-43.2%, p=0.001), and abdominal metastases (9%-28%, p=0.001) were significantly different between the groups.

Table 1. Comparison of clinical characteristics of patients according to groups

n=207		Grade 3 Endometrioid		Serous/ clear cell		p*
		Number	%	Number	%	
Cervical involvement	Yes	22	24,7	40	33,9	0,153
	No	67	75,3	78	66,1	
Adnexal involvement	Yes	12	13,5	37	31,4	**0,003**
	No	77	86,5	81	68,6	
Uterine serosal involvement	Yes	9	10,1	26	22,0	**0,023**
	No	80	89,9	92	78,0	
Lymphovascular space invasion	Yes	52	58,4	73	61,9	0,617
	No	37	41,6	45	38,1	
Cytology	Positive	9	10,1	35	29,7	**0,001**
	Negative	80	89,9	83	70,3	
Depth of myometrial invasion	<50	37	41,6	50	42,4	0,908
	≥50	52	58,4	68	57,6	
LN metastasis	Yes	18	20,2	51	43,2	**0,001**
	No	71	79,8	67	56,8	
Isolated pelvic LN metastasis	Yes	7	7,9	15	12,7	0,263
	No	82	92,1	103	87,3	
Isolated paraaortic LN metastasis	Yes	3	3,4	9	7,6	0,195
	No	86	96,6	109	92,4	
Abdominal metastasis	Yes	8	9,0	33	28,0	**0,001**
	No	81	91,0	85	72,0	

* Chi-square analysis was performed.

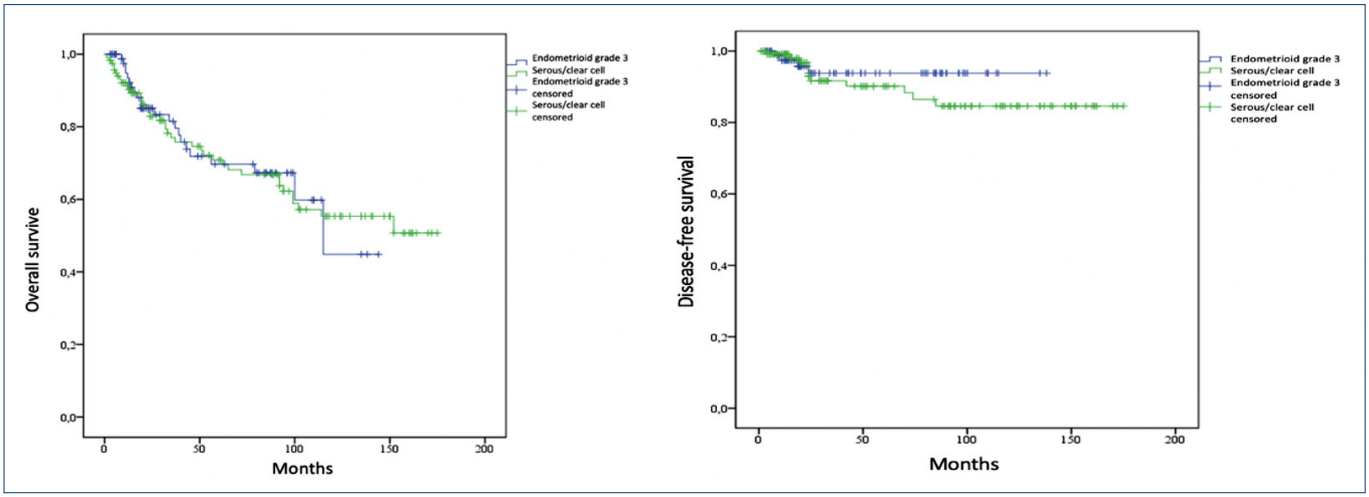

Figure 1. Overall survival and disease- free survival graphs according to groups

Table 2. Univariate and multivariate analyses for overall survival in all patients

n=207		Univariate analysis		Multivariate analysis		
		N of events (%)	p	HR	95% CI	p
Group	Grade 3 Endometrioid	22/89 (%75,3)	0,910			
	Serous/ clear cell	39/118 (%66,9)				
Age	≤63	23/97 (%76,3)	**0,039**	1,843	1,104-3,077	**0,019**
	>63	38/110 (%65,5)				
CA-125	≤35	39/146 (%73,3)	0,082			
	>35	19/50 (%62,0)				
Phase	Early stage	25/112 (%77,7)	**0,034**	1,849	1,098-3,111	**0,021**
	Late stage	36/95 (%62,1)				
Cervical involvement	There is	16/62 (%74,2)	0,226			
	No	45/145 (%69,0)				
Adnexal involvement	There is	16/49 (%67,3)	0,616			
	No	45/158 (%71,5)				
Uterine serosal involvement	There is	15/35 (%57,1)	0,146			
	No	46/172 (%73,3)				
Lymphovascular space invasion	There is	42/125 (%66,4)	0,182			
	No	19/82 (%76,8)				
Cytology	Positive	20/44 (%54,5)	0,232			
	Negative	41/163 (%74,8)				
Depth of myometrial invasion	<50	20/87 (%77,0)	0,090			
	≥50	41/120 (%65,8)				
LN metastasis	There is	23/69 (%66,7)	0,610			
	No	38/138 (%72,5)				
Isolated pelvic LN metastasis	There is	9/22 (%59,1)	0,378			
	No	52/185 (%71,9)				
Isolated paraaortic LN metastasis	There is	1/12 (%91,7)	0,141			
	No	60/195 (%69,2)				
Abdominal metastasis	There is	15/41 (%63,4)	0,449			
	No	46/166 (%72,3)				
Adjuvant treatment	Received	56/185 (%69,7)	0,658			
	Did not receive	5/22 (%77,3)				
Relapse	There is	9/15 (%40,0)	0,100			
	No	52/192 (%72,9)				

One hundred and eighty five (89.4%) patients received adjuvant treatment, of which 38 (20.5%) received radiotherapy (RT), 79 (42.7%) received chemotherapy (CT) and 68 (36.8%) received CT + RT. Recurrence was seen in 15 (7.2%) patients, 3 of them (20%) had local metastases and 12 of them (80%) had distant metastases and 61 (%29.4) of the patients died during the follow-up. While 43.8% of the grade 3 EEC group received RT, 10% received CT and 46.3% received RT + CT, 2.9% of the SEC/CCEC group received RT, 67.6% received CT and 29.5% received RT + CT and there was a significant difference in the type of adjuvant treatment between the groups ($p<0.001$). There was no significant difference between the groups in terms of adjuvant treatment status ($p=0.834$), recurrence status ($p=0.185$), localization of recurrence ($p=0.154$) and mortality ($p=0.193$).

In our study, the mean follow-up period was 40 months (range, 1-171 months), and during this follow-up period, 61 (%29.4) of 207 patients died from direct disease-related causes, and our overall survival rate during our follow-up period was 70.5%. The 12-month survival rate was 92.2%, 18-month survival rate was 88.8%, 24-month survival rate was 83.8% and 36-month survival rate was 78.8%. There was no significant difference in overall survival ($p=0.910$) or disease-free survival ($p=0.299$) between the groups (Figure 1).

Recurrence was observed in 15 (7.2%) of the 207 patients included in the study and the disease-free survival rate was 92.8%. When all patients were evaluated together, the mean survival time was 158.4. The 12-month survival rate was 98.4%, 18-month survival rate 97.7%, 24-month survival rate 96.3% and 36-month survival rate 92.5%.

According to univariate analysis, there was a significant risk for overall survival in age categories ($p=0.039$). According to the univariate analysis, there was a significant risk for overall survival between stages ($p=0.034$). A multivariate model was created for those who were significant in the univariate analysis and accordingly, age over 63 years and advanced stage were considered as poor prognostic factors (Table 2).

DISCUSSION

In the 2023 FIGO EC staging system, histopathological findings were redefined as prognostic risk factors. Histological type and tumor grade were categorized as aggressive/non-aggressive histology and low-grade/high-grade. In our study, we compared the clinicopathological features and prognostic factors of patients with uterine SEC/CCEC and grade 3 EEC, which constitute the aggressive group according to FIGO 2023 staging. We retrospectively analyzed the data of 207 patients with a follow-up period of up to 172 months (median follow-up period 40 months).

In one of the largest series in the literature comparing prognostic factors and outcomes of SEC and CCEC patients with grade 3 EEC; Hamilton et al. (8) studied 1478 patients with SEC, 391 with CCEC, and 2316 with grade 3 EEC, and found that a greater proportion of those with SEC or CCEC were diagnosed at an advanced stage (stage III-IV) than those with grade 3 EEC. The 5-year disease-specific survivals for women with SEC, CCEC, and grade 3 EEC were 55, 68, and 77%, respectively. On multivariate analysis, advanced disease ($p<0.001$), aggressive histology ($p<0.001$), and older age at diagnosis ($p<0.001$) were found to be independent prognostic factors for poor outcome. In our study, no significant difference was found in overall survival and disease-free survival rates between the grade 3 EEC and SEC/CCEC groups. In multivariate analysis, age > 63 and advanced stage disease were determined as poor prognostic factors.

In a meta-analysis examining a total of 6 studies including 11029 patients (4995 uterine carcinosarcoma, 4634 SEC, 1346 CCEC and 54 SEC or CCEC), it was seen that SEC and CCEC had a similar prognosis compared to other histological groups (9). Boruta et al. (10) retrospectively studied 52 grade 3 EEC and 87 SEC patients and found no significant difference between the two groups in terms of age, depth of MI, and LVSI (all P values < 0.05). Although these findings support our study, the rate of cervical involvement in SEC was lower in our study. When both groups were compared in terms of survival, no difference was found between advanced stage grade 3 EEC and SEC in terms of overall survival and disease-free survival, and SEC was found to have a worse prognosis in early stage patients. In the study by Ayeni et al. (11), in which they compared 119 grade 3 EEC, 211 SEC and 40 CCEC patients, they found no significant difference in overall survival between these 3 subgroups. Creasman et al. (12) retrospectively analyzed 148 SEC, 59 CCEC, and 325 grade 3 EEC patients and reported 5-year survival of 72% and 81% for early-stage SEC and CCEC, respectively; these results are similar to the 76% found for grade 3 EEC.

There are also studies in the literature that identify complete surgical staging and extent of LN dissection as other prognostic factors that may affect survival (13,14). In our study, except for 4 patients (patients who could not tolerate long surgery times due to their comorbidities), all 203 patients underwent surgical staging according to FIGO criteria. The literature has shown a survival advantage associated with comprehensive lymphadenectomy, and in light of this information we aimed to determine whether the extent of LN dissection and the presence of LN metastases contribute

to prognosis. According to our findings, the number of removed LN was not statistically different between the endometrioid and nonendometrioid groups. Additionally, we could not reveal the effect of the number of removed LN and the presence of LN metastasis on survival.

CONCLUSION

According to our findings, no significant difference was found in overall survival and disease-free survival rates between the grade 3 EEC and SEC/CCEC groups. In multivariate analysis, age > 63 years and advanced stage disease were determined as poor prognostic factors in both groups. There is no consensus in the literature regarding the prognosis of these three high-risk endometrial cancers that we examined, therefore, studies with larger patient populations are needed to clearly determine the prognostic factors affecting survival.

Conflict of interest
The authors have no conflicts of interest to report.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Hematolojik belirteçler preoperatif dönemde endometriyal intraepitelyal neoplazi ve grade 1 endometrioid endometriyal karsinom arasındaki farkı predikte etmede yardımcı mıdır?

Are hematological markers helpful in predicting the difference between endometrial intraepithelial neoplasia and grade 1 endometrioid endometrial carcinoma in the preoperative period?

Mete SARGIN[1], Mustafa ŞAHİN[2], Hakan Raşit YALÇIN[3]

[1]Prof. Dr. Alaeddin Yavaşca Devlet Hastanesi, Kilis, Türkiye
[2]Jinekolojik Onkoloji Cerrahisi Kliniği, Ankara Şehir Hastanesi, Ankara, Türkiye
[3]Jinekolojik Onkoloji Cerrahisi Kliniği, Ankara Şehir Hastanesi, Ankara, Türkiye

ÖZ

Amaç: Sistemik inflamatuar belirteçlerin endometrial intraepitelyel neoplazili ve grade 1 endometrioid tip endometrium kanserli hastalardaki farkı predikte etmedeki rolünü değerlenmektir.

Gereç ve Yöntemler: Eylül 2019- Temmuz 2023 tarihleri arasında tersiyer bir merkezde preoperatif endometrial biyopsi sonucu EİN olan 75 hasta ve grade 1 endometrioid tip endometrial kanser olan 223 hasta olmak üzere toplam 298 hastanın verileri hastane veri tabanından retrospektif olarak incelendi. İki grup arasındaki klinik ve biyokimyasal sonuçlar karşılaştırıldı.

Bulgular: Endometrial intraepitelyal neoplazili ve grade 1 endometrioid tip endometrium kanserli hasta grupları arasında yaş ve inflamatuar prognostik indeks değerleri arasındaki fark istatistiksel olarak anlamlıydı(sırasıyla p<0.001 ve p=0.006). Hasta grupları arasında nötrofil, lenfosit, monosit, platelet, nötrofil/lenfosit oranı, platelet/lenfosit oranı, C-reaktif protein, albumin, Glasgow Prognostik Skoru, Prognostik Nutrisyonel İndeks değerleri açısından istatistiksel olarak anlamlı farklılık yoktu.

Sonuç: İnflamatuar prognostik indeks, endometrial intraepitelyel neoplazili ve grade 1 endometrioid tip endometrium kanserli hastaların preoperaptif ayırt edilmesine yardımcı olabilir. Ancak bu sonucun desteklenip günlük pratiğimizde yer alması için daha kapsamlı çalışmalar gereklidir.

Anahtar Kelimeler: Hematolojik paremetreler, inflamatuar prognostik indeks, endometrial intraepiteliyal neoplazi, endometrial kanser

ABSTRACT

Aim: To evaluate the role of hematological markers in preoperatively predicting the difference in patients with endometrial intraepithelial neoplasia and grade 1 endometrioid type endometrial cancer.

Materials and Methods: The data of a total of 298 patients, including 75 patients with EIN as a result of preoperative endometrial biopsy and 223 patients with grade 1 endometrioid type endometrial cancer in a tertiary center between September 2019 and July 2023, were retrospectively examined from the hospital database. Clinical and biochemical results were compared between the two groups.

Results: The difference between age and inflammatory prognostic index values between the patient groups with endometrial intraepithelial neoplasia and grade 1 endometrioid type endometrial cancer was statistically significant (p<0.001 and p=0.006, respectively). There was no statistically significant difference between the patient groups in terms of neutrophil, lymphocyte, monocyte, platelet, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, C-reactive protein, albumin, Glasgow Prognostic Score, Prognostic Nutritional Index values.

Conclusion: Inflammatory prognostic index may support the preoperative discrimination of patients with endometrial intraepithelial neoplasia and grade 1 endometrioid type endometrial cancer. However, more comprehensive studies are required to support this result and include it in our daily practice.

Keywords: Hematological markers, inflammatory prognostic index, endometrial intraepithelial neoplasia, endometrial cancer

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Sorumlu Yazar/Corresponding Author: Mustafa ŞAHİN, Ankara Şehir Hastanesi, Jinekolojik Onkoloji Cerrahisi Kliniği, Çankaya, Ankara, Türkiye
E-mail: mustafasahin1163@gmail.com

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GİRİŞ

Endometrium kanseri gelişmiş ülkelerde görülen en sık jinekolojik kanserdir. Premalign endometrial lezyonların zamanında tanı alabilmesi ve risk faktörlerinin azaltılması ile endometrium kanserlerinin azalabilir (1).Endometrial patolojiler benign, premalign, malign lezyonlar olarak üç kategoriye ayrılır ve premalign lezyonlar endometrial intraepitelyal neoplazi (EİN) olarak tanımlanır (2). Dünya Sağlık Örgütü'nün 1994 sınıflandırmasına göre kanser progresyonunu daha iyi göstermesi ve tanı kriterlerindeki objektif özelliklerinden ötürü EIN sınıflaması öne çıkmaktadır (3).

Semere ve ark.(4) EİN tanısı alan örneklerin %15'ine endometrial kanser eşlik ettiği saptadı. Salman ve ark.(5) da nihai patolojisi endometrial kanser olan hastaların yaklaşık %25'inde frozen incelemede kanser saptanmadığını belirtti. Bu durum endometrial kanserli hastaların preoperatif dönemle EIN hastalarından ayrımını yapmada farklı yöntemlerin geliştirilmesi ihtiyacını doğurdu.

Kanser ve inflamasyon ilişkisi ilk kez 19. yüzyılda Virchow'un çalışmalarında değerlendirildi. Balkwill ve ark.(6) kronik inflamasyon gerçekleşen kanserlerde lökosit artışını görüldükten sonra, lökositlerin tümöral büyümeye destek sağladığını öne sürdü. Kanser ve inflamasyon konusunda yapılan çalışmalar sonucunda intrensek ve ekstrensek mekanizmalar ile kanser oluşumu tanımlandı. İntrensek mekanizma, kanser oluştuktan sonra dokuda inflamasyon yanıtı oluşması ve sonrasında kanserli dokunun büyümesinin indüklenmesi: Ekstrensek mekanizma ise, mevcut olan kronik inflamasyonun kanser oluşumunu desteklemesi olarak açıklandı (7). Endometrium kanserlerinde tümör büyümesinde intrensek mekanizmanın etkin olduğu düşünülmektedir. Srivastava ve ark.(8). rahim içi araç kullanımına bağlı gelişen endometrial dokudaki lökosit artışı ve inflamatuar ortamın, endometrial kanser insidansında artışa neden olmadığını gösterdi.

Bacanakgil ve ark.(9) nötrofil lenfosit oranının (NLO) ortalama sınır değeri 4 ve üzeri değerler aldıklarında anormal uterin kanama izlenen hastalarda malign endometrial patoloji olma ihtimalini saptayabileceğini gösterdi. Platelet/lenfosit oranı(PLO) inflamasyonun sensitif göstergesi olup, kanserli hastalarda saptanan inflamatuar süreçte artan trombosit, azalan lenfosit sonucu, PLO değerinde artış ve kötü prognoz ile ilişkili olabilir (9) C-reaktif protein/albümin oranı(CAR), birçok hastalık durumunda prognostik belirteç kabul edilmektedir. Bir akut faz proteini olarak CRP'nin artması, kolorektal kanserler dahil olmak üzere birçok kanserde prognoz göstergesi olduğu bildirilmiştir. Albümin, negatif bir akut faz reaktanıdır ve CRP'nin artmasıyla serum albümin miktarı düşmektedir (10). Dirican ve ark.(11) inflamatuar prognostik indeksin erken ve ileri evre küçük hücreli dışı akciğer kanserleri predikte etmedeki rolünü değerlendirdi. Küçük hücreli dışı akciğer kanserlerinin inflamatuar prognostik indeks değerlendirilmesi ile sağ kalım arasında anlamlı fark saptandı.

Çalışmamızda endometrial intraepitelyal neoplazi ve grade 1 endometrioid endometrial adenokanserin iflamatuar sürece etkisini değerlendirebilmek amacı ile sistemik inflamatuar belirteçleri ele alınarak, kanseri predikte etme açısından etkinliklerini değerlendirmeyi amaçlıyoruz.

GEREÇ VE YÖNTEM

Eylül 2019- Temmuz 2023 arasında Ankara Bilkent Şehir Hastanesi, Jinekolojik Onkoloji Cerrahisi kliniğinde preoperatif endometrial biyopsi sonucu EİN olan 75 hasta ve grade 1 endometrioid tip endometrial adenokanser olan 223 hasta olmak üzere, opere olan toplam 298 hastanın verileri retrospektif olarak elde incelendi. Veriler elektronik veri tabanı sisteminden, hasta dosyalarından, patoloji raporlarından ve ameliyat notlarından elde edildi. Çalışma için Ankara Bilkent Şehir Hastanesi 2 Nolu Klinik Araştırmalar Etik Kurul Başkanlığından 01.03.2023 tarihli E2-23-3464 etik kurul kararı ile onayı alındı.

Hematolojik paremetreleri ve patoloji preparatları hastanemizde değerlendirilen, nihai patolojide EİN veya grade 1 endometrioid tip endometrial adenokarsinom histolojisinde olan, hematolojik-immünolojik parametrelerde değişikliğe neden olabilecek ek hastalığı ya da ilaç kullanım öyküsü olmayan, preoperatif bir haftada öncesine kadar hematolojik paremetreleri bakılmış olan hastalar çalışmaya dahil edildi. Her hasta için preoperatif patolojik tanı ve postoperatif patolojik tanı birlikte değerlendirildi ve her hasta için kesin histopatolojik tanı belirlendi. Histopatolojik incelemelerinin hastanemizde değerlendirilmemiş olması ve verilerin eksik olması dışlama kriterleri arasında yer aldı.

Bu amaçla; Nötrofil/lenfosit oranı (NLO), Platalet/lenfosit oranı (PLO), C-reaktif protein/ albumin (CAR), Glosgow prognostik skoru (GPS), Prognostik nütrisyonel indeks (PNİ) ve İnflamatuar prognostik indeks(İPİ) gibi parametreler ele alındı.

Modifiye Glosgow prognostik skoru (mGPS) için CRP yüksekliği (> 1.0 mg/dl) ve hipoalbüminemisi (< 3.5 mg/dl) olan hastalara 2 puan, yalnızca CRP'si yüksek olanlara 1 puan ve albümin düzeylerinden bağımsız olarak CRP'si normal olanlara 0 puan verilir (12). Prognostik nütrisyonel indeks (PNİ): Serum albümini (Alb) (g/L) + 5 x toplam lenfosit sayısı (10^9/L) olarak hesaplanır (13). İnflamatuar prognostik indeks(İPİ): C-reaktif protein × NLO (nötrofil/lenfosit oranı)/serum albümini olarak hesaplanır (11).

İstatistiksel Analiz

Çalışmada yer alan yaş, nötrofil, lenfosit, monosit, platelet, NLO, CRP, PLO, albumin, GPS, PNİ, İPİ değerleri gibi sürekli değişkenlerin normal dağılıma uygunluğu 30 grafiksel olarak ve Shapiro-Wilks testi ile değerlendirildi. Sürekli değişkenlerin yaş değeri hariç normal dağılıma uymadıkları belirlendi. Değişkenlerin tanımlayıcı istatistiklerinin gösteriminde ortalama±ss (standart sapma) ve medyan (minimum-maksimum) değerleri verildi. EIN ve G1 endometrioid tip adenokarsinom gruplarının nötrofil, lenfosit, monosit, platelet, NLO, CRP, PLO, albumin, GPS, PNİ, İPİ değerlerinin karşılaştırılmasında Mann- Whitney U testi kullanıldı. EIN ve G1 endometrioid tip endometrial adenokarsinom gruplarının yaş değerinin karşılaştırılmasında ise Bağımsız Örneklem t testi kullanıldı. İstatistiksel analizler ve hesaplamalar için IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) ve MS-Excel 2007 programları kullanılmıştır. İstatistiksel anlamlılık düzeyi $p<0.05$ olarak kabul edildi.

BULGULAR

Final patoloji sonucuna göre hastalar 2 gruba ayrıldı. EIN olan 75 hasta ve grade 1 endometrioid tip endometrial adenokanser (G1) olan 233 hasta çalışmaya dahil edildi. Çalışmaya dahil edilen 298 hastanın 96'sı (%32.2) premenopozal, 202'si (%67.8) postmenopozaldi. EİN grubunun yaş ortalaması 51.76±8.95 yıl, G1 grubunda ise 58.36±10.87 yıl olup, yaş değerleri açısından gruplar arasında istatistiksel olarak anlamlı farklılık vardı (t=4.745, p<0.001) (Tablo 1) (Şekil 1).

Vücut kitle indeksi, açlık kan şekeri, parite, ve ek hastalık (HT, DM) varlığı açısından gruplar arasında fark yoktu (p>0.05).

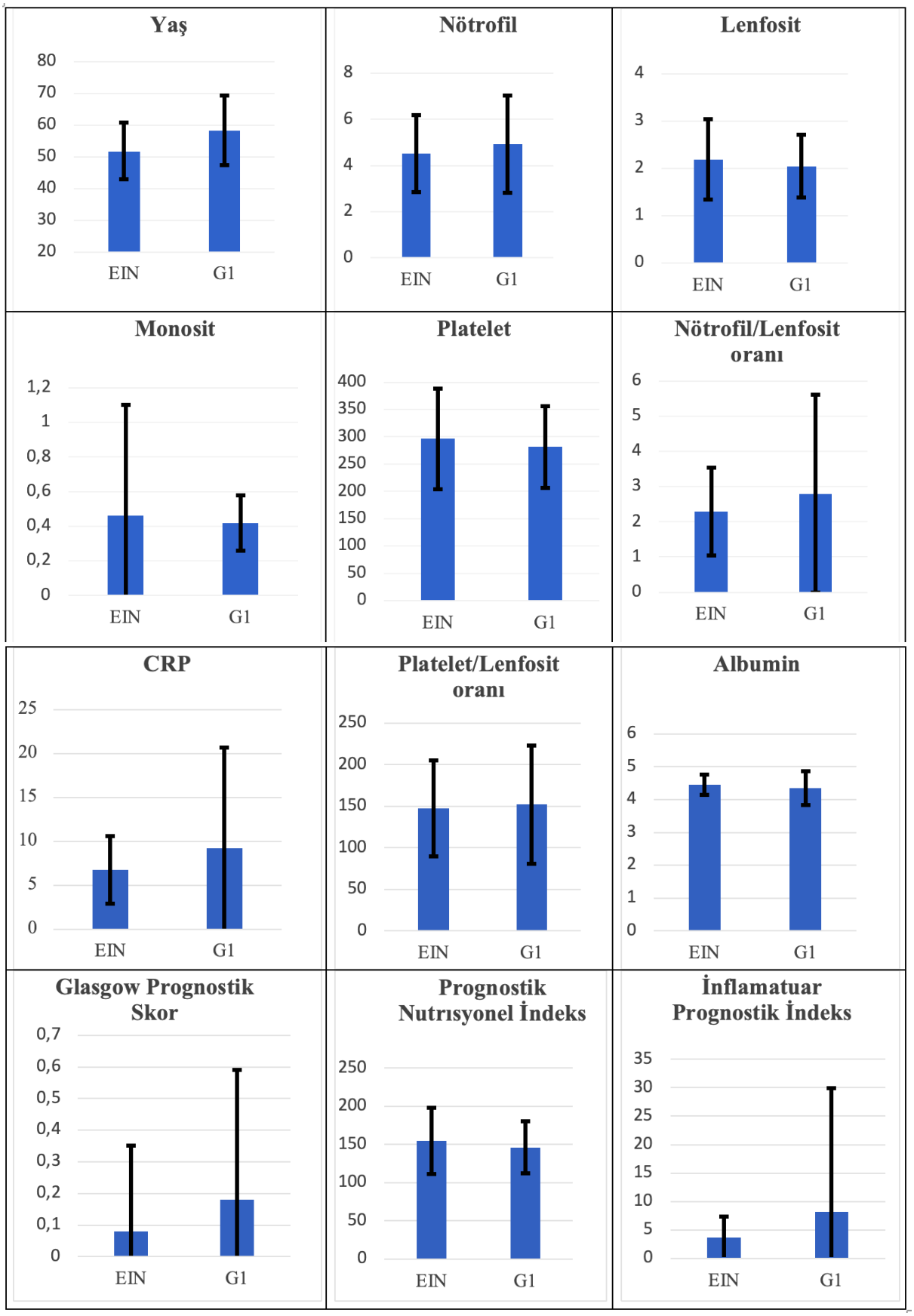
EİN ve G1 grupları arasında nötrofil (z=1.102, p=0.270), lenfosit (z=0.948, p=0.343), monosit (z=0.857, p=0.391), platelet (z=1.083 p=0.279), NLO (z=1.527, p=0.127), CRP (z=1.905, p=0.057), PLO (z=0.248, p=0.804), albumin (z=0.918, p=0.358), Glasgow Prognostic Skoru (z=1.945,p=0.052), Prognostic Nutrisyonel İndex (z=1.055, p=0.291) değerleri açısından istatistiksel olarak anlamlı farklılık saptanmadı (Tablo 1) (Şekil 1).

Inflamatuar Prognostik İndeks(İPİ) ortalaması EIN grubunda 3.62± 3.78, G1 grubunda ise 8.18± 21.72 idi. EIN ve G1 grupları arasında İPİ değerleri açısından istatistiksel olarak anlamlı farklılık tespit edildi (z=2.746, p=0.006) (Tablo 1) (Şekil 1).

Tablo 1. Gruplara göre parametrelerin karşılaştırılması

	EIN (n=75)		G1 (n=223)		Test İstatistiği	
	Ort±SS	Medyan (Min-Max)	Ort±SS	Medyan (Min-Max)	z; t	p
Yaş	51.76±8.95	51.0 (31.0-73.0)	58.36±10.87	58.0 (28.0-84.0)	t=4.745	**<0.001**
Nötrofil	4.52±1.67	4.29 (0.30-9.63)	4.93±2.11	4.40 (1.57-13.19)	z=1.102	0.270
Lenfosit	2.19±0.85	2.03 (0.69-5.74)	2.05±0.66	2.02 (0.35-3.84)	z=0.948	0.343
Monosit	0.46±0.64	0.38 (0.18-5.83)	0.42±0.16	0.39 (0.15-1.35)	z=0.857	0.391
Platelet	296.53±92.23	287.0 (77.0-631.0)	281.51±74.71	273.0 (80.0-556.0)	z=1.083	0.279
N/L	2.29±1.25	2.00 (0.11-9.80)	2.80±2.81	2.17 (1.05-36.37)	z=1.527	0.127
CRP	6.75±3.83	5.00 (0.70-21.44)	9.24±11.46	5.90 (0.70-110.0)	z=1.905	0.057
P/ L	147.41±57.93	144.52 (62.8-418.5)	152.01±71.15	138.1 (38.4-808.5)	z=0.248	0.804
Albumin	4.45±0.31	4.50 (3.60-5.10)	4.35±0.52	4.50 (1.00-5.90)	z=0.918	0.358
GPS	0.08±0.27	0.0 (0.0-1.0)	0.18±0.41	0.0 (0.0-2.0)	z=1.945	0.052
PNİ	154.47±43.13	144.5 (77.5-332.0)	146.05±34.03	145.5 (54.5-233.0)	z=1.055	0.291
İPİ	3.62±3.78	2.81 (0.22-25.84)	8.18±21.72	3.54 (0.28-212.14)	z=2.746	**0.006**

n; hasta sayısı: Ort±SS; ortalama±standart sapma: Min-Max; minimum-maksimum; EIN: Endometrial İntraepitelyal Neoplazi; G1 : Grade 1 Endometrioid Endometrial Adenokarsinom; z: Mann Whitney U Test İstatistiği; t: Bağımsız Örneklem t Test İstatistiği; N/L: Nötrofil/Lenfosit Oranı ;P/L: Platelet/Lenfosit Oranı; GPS: Glasgow Prognostic Skor; PNI: Prognostic Nutrisyonel İndeks ;İPİ: Inflamatuar Prognostik İndeks



EIN: Endometrial İntraepitelyal Neoplazi; G1: Grade 1 Endometrioid Endometrial Adenokarsinom

Şekil 1. Parametrelerin gruplara göre dağılımı

TARTIŞMA

Endometrium kanseri gelişmiş ülkelerde kadınlarda en fazla tanı alan jinekolojik kanserdir. Hem çevresel hem de hastaya özgü risk faktörleri sebebiyle insidansı artmaktadır. Tanıda semptomatik hastalarda ultrasonografi, MR gibi non invaziv yöntemler yardımcı olsa da esas tanısı histopatolojik olarak konulmaktadır.

Kanser ve inflamasyonun ilişkisini gösteren çalışmalar özellikle son yıllarda artış göstermektedir. İnflamasyon belirteçleri olarak hastaların periferik venöz kanından alınan örneklerde saptanan hematolojik parametrelere vurgu yapılmaktadır (14).

Yaş, endometrial hiperplazi ve endometrial kanser için yaş önemli bir risk faktörüdür. Çalışmamızda endometrium kanseri tanısı alan hastaların %80' i 55 yaş üzeri postmenopozal kadınlardı. Ural ve ark. (15) çalışmasında yaş, endometrium kanseri ve endometrial hiperlazi saptanan gruplar arasında anlamlı bir değişken olarak bulundu (p<0.001). Çalışmamızda benzer şekilde EIN ve grade 1 endometrioid endometrial adenokanserli hastaları arasında yaş açısından istatistiksel anlamlı farklılık vardı (p<0.001). EIN grubundaki hastaların, GI endometrioid endometrial adenokanser olgularından daha genç yaşta tanı alması güncel literatür ile uyumludur.

Kanser gelişimi sonrasında gelişen inflamatuar yanıt ve bununla ilişkili salınan sitokinler aracılığıyla, hastalarda nötrofil sayısında artma, lenfosit sayısında azalma, platelet sayısında ve boyutunda artma gözlenebilmektedir. Yapılan çalışmalarda nötrofil/lenfosit oranının ve platelet/lenfosit oranının, inflamasyonun güçlü bir göstergesi ve malignite açısından prediktif değeri olduğu belirtilmektedir. İnflamasyon ve kanser arasındaki ilişkinin aydınlatılması sonrası birçok çalışmada bu parametreler ile kanserin tanısı ve prognozu üzerine çalışmalar yapılmıştır.

Ural ve ark. (16) çalışmasında endometrium kanseri grubunda endometrial hiperplazi grubuna kıyasla nötrofil/lenfosit oranı(NLO) açısından anlamlı farklılık tespit etti (p= 0.024). Çalışmamızda NLO grade 1 endometrioid endometrial kanser grubunda daha yüksekti ancak EIN grubuna kıyasla NLO açısından anlamlı farklılık yoktu.

Kronik inflamasyon sonucunda kanserli hastalarda azalmış PLO değerleri görülmektedir (17). Açmaz ve ark.(18) PLO açısından endometrium kanserli hasta grubuna kıyasla endometrial hiperplazili hasta grubunda istatistiksek olarak anlamlı farklılık buldu(p< 0.001). Aksine Ural ve ark.' nın (15) çalışmasında endometrium kanserli hasta grubuna kıyasla endometrial hiperplazili hasta grubunda istatistiksek olarak anlamlı farklılık yoktu. Bizim çalışmamızda da grade 1 endometrioid endometrial kanser grubuna kıyasla EIN grubunda PLO açısından anlamlı farklılık saptanmadı (p= 0.804).

Temur ve ark.(18) NLO' nun kanserli hastalarda sağkalım için prognostik bir faktör olduğu belirlenmiş, ayrıca NLO ve PLO' nun endometrial kanserde lenf nodu tutulumu ve serviks invazyonu için prediktif bir değer olduğu saptanmıştır.

Glasgow Prognostik Skor(GPS)' un kolon ve rektum kanseri rezeksiyonu sonrası genel ve hastalığa özgü sağkalım süresini predikte etmedeki önemi bazı çalışmalarda gösterildi (19). Saijo ve ark.(20) GPS'nin endometrium kanseri olan hastalarda tümör evresi ve miyometrial invazyon açısından istatistiksel olarak anlamlı olduğunu buldu (sırasıyla p= 0.001, p=0.016). Çalışmamızda bunun aksine GPS'i açısından grade 1 endometrioid endometrial kanser grubuna kıyasla EIN grubunda istatistiksek olarak anlamlı farklılık yoktu (p= 0.052).

Kim ve ark.(21) endometrium kanseri cerrahisi öncesinde yüksek PNİ'ye sahip hastalarda, düşük PNİ'ye sahip hastalara kıyasla kansere özgü ölüm oranının daha düşük olduğunu gösterdi. Haraga ve ark.(22) da düşük PNİ değerlerinin serviks kanserinde kötü prognoz ile ilişkili olduğunu gösterdi. Çalışmamızda ise EIN grubunda daha yüksek PNİ değerleri saptanmış olmasına rağmen, prognostik göstergeyi kanserogeneze uyarlama konusunda literatüre uyumlu sonuçlar elde edilememiştir (p=0.291).

Dirican ve ark.(11) düşük İPİ ile karşılaştırıldığında yüksek İPİ değerlerinin ileri yaş, daha büyük tümör boyutu, yüksek lenf nodu tutulumu, uzak metastaz, ileri evre ve kötü performans durumu ile ilişkili olduğunu buldu. Yüksek İPİ değerlerinde progresyonsuz sağkalım değeri anlamlı olarak düşüktü (p <0.001). Erdoğan ve ark. (23) hormon reseptör pozitif olan metastatik meme kanserlerinde progresyonsuz sağ kalımın yüksek İPİ değerlerine sahip hasta grubunda daha az olduğu buldu. Çalışmamızda benzer şekilde grade 1 endometrioid endometrial adenokarsinom grubunda İPİ yüksekliği istatistiksel olarak anlamlıydı (p= 0.006).

Çalışmamızın retrospektif olması temel sınırlayıcı faktördür. Tek merkezden verilerin toplanması, patoloji verileri için nihai raporların kullanılması, geniş hasta örneklemine sahip olması ise çalışmanın avantajlarıdır.

SONUÇ

Çalışmamızın sonucunda ve güncel literatür tecrübesinde, sistemik inflamatuar belirteçlerin teorikte gösterilen faydasına rağmen, bu belirteçlerin günlük çalışma pratiğimizde henüz yer edinemediğini gözlemlemekteyiz. Üzerinde çalışılan sistemik inflamatuar belirteçlerin kapsamı ve içerik tanımlamalarının daha kapsamlı çalışmalar ile netleştirilmesi gerekmektedir.

Yazar Katkıları
Yazarların çalışmadaki katkı oranları eşittir.

Destek
Çalışma herhangi bir destek almamıştır.

Çıkar Çatışması Beyanı
Çalışma kapsamında yazarlar arasında, herhangi bir kurum veya kişi ile çıkar çatışması bulunmamaktadır.

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Clinicopathological disparities between superficial and vanishing endometrial cancer

Yüzeyel ve kaybolan endometrial kanser arasındaki klinikopatolojik farklılıklar

Mehmet TUNÇ[1], Tuğba TEKELİOĞLU[2], Ezgi KARAPINAR[3], Sefa Çağlar ÖZDAL[3], Emre BAYRAKTAR[3], Neşe Selin MİRZA[3], Hüseyin AKILLI[1], Esra KUŞÇU[1]

[1]Başkent University, School of Medicine, Department of Gynecology and Obstetrics, Ankara, Türkiye
[2]Samsun Training and Research Hospital, Department of Gynecology and Obstetrics, Samsun, Türkiye
[3]Başkent University, School of Medicine, Ankara, Türkiye

ABSTRACT

Aim: This study aims to compare the clinicopathological characteristics and oncologic outcomes of patients with vanishing endometrial cancer (VEC) and superficial endometrial cancer (SEC).

Materials and Methods: A retrospective analysis was conducted on 130 patients diagnosed with stage IA endometrial cancer who underwent surgery at Başkent University School of Medicine from 2007 to 2023. Data including age, body mass index (BMI), histopathological type, lymphovascular space invasion, and survival outcomes were collected. Statistical analyses were performed using IBM SPSS version 25.0.

Results: Among the 130 patients, 40 (30.8%) had VEC and 90 (69.2%) had SEC. The median age was 55 years, and the median follow-up was 74.5 months. The 5-year DFS and OS rates were 99.2% and 97.5%, respectively, with no significant differences between the groups. Patients with VEC were younger and had a lower mean BMI compared to those with SEC. Rates of endometrial intraepithelial neoplasia and hyperplasia were similar across the groups.

Conclusion: VEC is a rare entity that requires surgical intervention, as a significant proportion of patients exhibit hyperplasia or EIN in surgical specimens. The comparable survival outcomes for VEC and SEC suggest that current management strategies can yield favorable prognoses for both, emphasizing the need for careful monitoring to avoid undertreatment of VEC cases.

Keywords: Vanishing endometrial cancer, early-stage, superficial endometrial cancer, residual endometrial cancer, survival

ÖZ

Amaç: Bu çalışmanın amacı, kaybolan endometrial kanser (KEK) ve yüzeyel endometrial kanser (YEK) hastalarının klinikopatolojik özelliklerini ve onkolojik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: 2007-2023 yılları arasında Başkent Üniversitesi Tıp Fakültesi'nde ameliyat olan evre IA endometrial kanser tanısı almış 130 hasta üzerine retrospektif olarak analiz edilmiştir. Yaş, vücut kütle indeksi (VKİ), histopatolojik tür, lenfovasküler alan invazyonu ve sağkalım sonuçları gibi veriler toplanmıştır. İstatistiksel analizler IBM SPSS sürüm 25.0 kullanılarak yapılmıştır.

Bulgular: Toplam 130 hastadan 40'ının (30.8%) KEK, 90'ının (69.2%) ise YEK olduğu tespit edilmiştir. Medyan yaş 55 yıl olup, medyan takip süresi 74.5 aydır. Beş yıllık hastalıksız sağkalım ve toplam sağkalım oranları sırasıyla %99.2 ve %97.5 olup, gruplar arasında anlamlı bir fark bulunmamıştır. KEK hastalarının, YEK hastalarına kıyasla daha genç ve daha düşük ortalama VKİ'ye sahip olduğu belirlenmiştir. Endometrial intraepitelyal neoplazi ve hiperplazi oranları gruplar arasında benzer orandadır.

Sonuç: KEK, cerrahi müdahale gerektiren nadir bir durumdur, çünkü hastaların önemli bir kısmında cerrahi örneklerde hiperplazi veya EIN tespit edilmektedir. KEK ve YEK için karşılaştırılabilir sağkalım sonuçları, mevcut yönetim stratejilerinin her iki grup için de olumlu prognoz sağladığını göstermektedir; bu nedenle, KEK vakalarında yetersiz tedaviden kaçınmak için yakın takip gerekmektedir.

Anahtar Kelimeler: Kaybolan endometrial kanser, erken evre, yüzeyel endometrial kanser, rezidüel endometrial kanser, sağkalım

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Sorumlu Yazar/Corresponding Author: Mehmet TUNÇ, Başkent University, School of Medicine, Department of Obstetrics and Gynecology, Şehit Temel Kuğuoğlu Cd. No: 34/A, 06490, Bahçelievler, Ankara, Turkey
E-mail: mhmttunc@gmail.com

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INTRODUCTION

Endometrial cancer (EC) is the second most common gynecological cancer, following cervical carcinoma, according to GLOBOCAN 2022 (1). The incidence of EC rising due to factors such as obesity, age, and lifestyle changes. EC is broadly classified into two subtypes: type 1 and 2. Type 1 tumors primarily consist of endometrioid carcinoma and are associated with unopposed estrogen stimulation, while type 2 encompasses more aggressive histological forms, such as serous and clear cell carcinomas (2).

Diagnosis of EC is based on pathological examination of endometrial samples. Occasionally, no EC is found in hysterectomy specimen despite a definitive diagnosis of cancer in endometrial biopsy specimen; this phenomenon is referred to as vanishing endometrial cancer (VEC) (3-5). Vanishing carcinoma is a rare entity characterized by significant cytological atypia with minimal tumor volume, first described in 1995 by Goldstein et al. in the context of prostate cancer (6). Additionally, superficial endometrial cancer (SEC) describes localized disease confined to the endometrium.

Despite the growing body of literature surrounding these malignancies, notable gaps exist in comparative studies that thoroughly investigate the clinical and pathological features influencing patient outcomes. Given the distinct trajectories of type 1 and 2 EC, understanding the differences between VEC and SEC could have significant implications for treatment and prognosis. Therefore, this study aimed to compare SEC and VEC in terms of clinicopathological factors and to demonstrate oncologic outcomes between the two groups.

MATERIALS AND METHODS

Patients with EC who underwent surgery in Başkent University School of Medicine, Department of Obstetrics and Gynecology were retrospectively investigated from 2007 to 2023. The study was approved by Başkent University Institutional Review Board (KA23/192). Data including age, histopathological type, chemotherapy administration, comorbid diseases, parity, body mass index (BMI), menopausal status, presence of p53 mutation, lymphovascular space invasion (LVSI), recurrence and survival patterns were collected from the patient files and hospital data.

Preoperative endometrial samples for the diagnosis of EC were obtained via using 3 different instruments: dilatation and curettage (D&C), hysteroscopic biopsy, and pipelle biopsy. In D&C, the cervix is dilated, and uterus is scraped with a sharp curette and aspirated with a Karman cannula. In hysteroscopy, the tissue samples are collected using a thin, flexible telescope. The pipelle method employs a suction mechanism and requires no cervical dilation. Histopathological examinations were conducted by 2 gynecologic pathologists according to current guidelines.

Inclusion criteria consisted of patients who underwent total abdominal hysterectomy (TAH) and/or bilateral salpingo-oophorectomy (BSO) at Başkent University Ankara Hospital, with stage IA EC confined to the endometrium and no lymphatic metastasis. Both type 1 and type 2 EC patients were included, with type 1 referring to endometrioid adenocarcinoma and type 2 to serous, clear cell, and mixed carcinomas. Patients exhibiting myometrial invasion, cervical involvement, or distant metastasis were excluded. Additionally, those who received radiotherapy, chemotherapy, and fertility-sparing treatment between diagnosis and hysterectomy were also excluded.

Statistical analysis was conducted using IBM SPSS ver. 25.0 for Windows. Categorical variables were described as percentages, while continuous variables were presented as means and medians. Fisher's Exact test and Chi-Square tests were utilized when appropriate. The Kaplan-Meier survival test assessed disease-free survival (DFS) and overall survival (OS). A P-value less than 0.05 was deemed statistically significant.

RESULTS

A total of 134 patients were investigated retrospectively, with 130 patients included in this study. The median age was 55.0 years (range:33-87). The median follow-up was 74.5 months (range:1-192). Forty patients (30.8%) had VEC, while 90 patients (69.2%) had SEC. Demographic characteristics of the patients between groups are presented in Table 1.

Seventy-three patients (56.2%) presented with postmenopausal bleeding, followed by abnormal uterine bleeding (n:39, 30.0%). Sixty-five patients (50.0%) had tumor arising in polyps. Disease characteristics of the patients between groups are summarized in Table 2.

A total of 121 patients (93.1%) underwent lymph node dissection, while 9 patients (6.9%) had only TAH-BSO. The mean number of lymph nodes extracted was 38.4 (range:8-73). Seven patients (5.4%) received adjuvant chemotherapy. Most patients in both groups had type 1 EC (85.0% and 82.2%, respectively; p: 0.317). Surgical and tumor characteristics between groups are detailed in Table 3. The 5-year DFS and OS were 99.2% and 97.5%, respectively, with no significant differences is DFS or OS noted between groups (p: 0.157 and 0.218, respectively). The Kaplan-Meier survival plots for DFS and OS are illustrated in Figure 1.

Table 1. Characteristics of the Patients

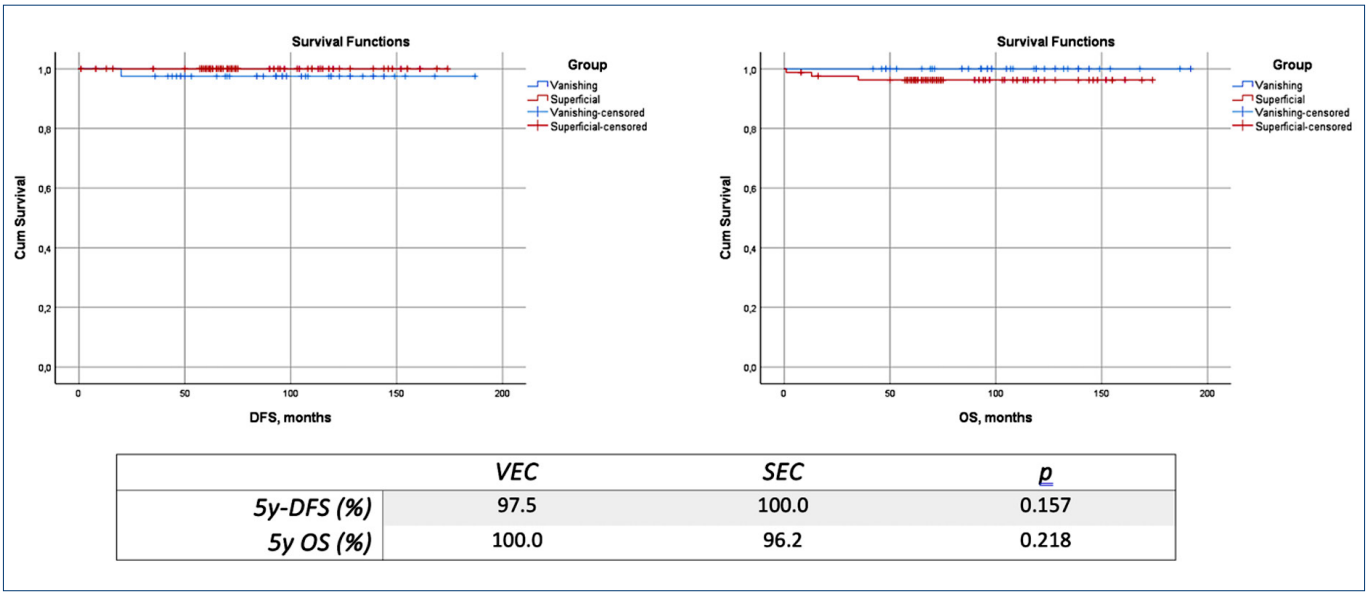
	Vanishing (n:40)	Superficial (n:90)	P
Age, median (years)	55.5 (33-77)	57.0 (34-87)	**0.036**
Parity, mean	2.84 (0-9)	2.78 (0-11)	0.899
Menopausal Status			
Yes (%)	16 (40.0)	23 (25.6)	0.103
No (%)	24 (60.0)	67 (74.4)	
BMI, mean (kg/m²)	30.3 (22.2-47.3)	34.0 (19.6-68.1)	**0.046**
Follow-up, median (months)	98.0 (42-192)	71.0 (1-174)	**0.007**

Abbreviations: BMI: Body-mass index

Table 2. Disease Characteristics of the Patients

	Vanishing (n:40) (%)	Superficial (n:90) (%)	P
Complaint			
PMB	16 (40.0)	57 (63.3)	**0.000**
AUB	14 (35.0)	25 (27.8)	
Pain	1 (2.5)	2 (2.2)	
Discharge	0 (0.0)	4 (4.4)	
None	7 (17.5)	0 (0.0)	
Missing	2 (5.0)	2 (2.2)	
Tumor Size, mean cm	1.72 (0.3-4.8)	2.47 (0.0-8.5)	0.117
Tumor Arising in Polyp			
Yes	20 (50.0)	45 (50.0)	0.145
No	20 (50.0)	40 (44.4)	
Missing	0 (0.0)	5 (5.6)	
Non-tumor Endometrium			
Normal	13 (32.5)	44 (48.9)	0.727
EIN	8 (20.0)	27 (30.0)	
Non-atypical Hyperplasia	3 (7.5)	17 (18.9)	
Missing	16 (40.0)	2 (2.2)	
Time Interval*, median, days	16.0	18.0	0.55

Abbreviations: EIN: Endometrial intraepithelial neoplasia
*Time interval between biopsy and surgery.



	VEC	SEC	p
5y-DFS (%)	97.5	100.0	0.157
5y OS (%)	100.0	96.2	0.218

Figure 1. DFS and OS plots of VEC vs SEC
Abbreviations: DFS: Disease-free survival, OS: Overall survival, VEC: Vanishing endometrial cancer, SEC: Superficial endometrial cancer

Table 3. Surgical and Tumoral Characteristics of the Patients

	Vanishing (n:40) (%)	Superficial (n:90) (%)	P
Surgery			
TAH-BSO	2 (5.0)	7 (7.8)	0.630
TAH-BSO+LND	38 (95.0)	83 (92.2)	
Histology			
Endometrioid	34 (85.0)	74 (82.5)	0.612
Serous	3 (7.5)	10 (11.1)	
Clear	1 (2.5)	3 (3.3)	
Carcinosarcoma	1 (2.5)	0 (0.0)	
Mixed	1 (2.5)	2 (2.2)	
Undifferentiated	0 (0.0)	1 (1.1)	
Adjuvant Treatment			
Yes	1 (2.5)	6 (6.7)	0.603
No	39 (97.5)	84 (93.3)	
Type			
I (Endometrioid)	34 (85.0)	74 (82.2)	0.317
II (Serous, Clear cell, Mixed)	6 (15.0)	16 (17.8)	
P53 mutation			
Negative	2 (5.0)	2 (2.2)	0.520
Positive	2 (5.0)	9 (10.0)	
Wild type	1 (2.5)	5 (5.6)	
Missing	35 (87.5)	74 (82.2)	
LVSI			
Negative	40 (100.0)	89 (98.9)	1.000
Positive	0 (0.0)	1 (1.1)	
No of LNs, mean (range)	39.7 (12-71)	37.7 (8-73)	0.425

Abbreviations: TAH: Total abdominal hysterectomy, BSO: Bilateral salpingooophorectomy, LND: Lymph node dissection, No of LNs: Number of lymph nodes

DISCUSSION

This study presents a comprehensive retrospective analysis of 130 patients diagnosed with stage IA EC, comprised of 40 with VEC and 90 with SEC. The demographic and disease characteristics demonstrate a significant cohort with varied presentations, predominantly experiencing postmenopausal and abnormal uterine bleeding, underscoring the need for vigilance in diagnosing EC among postmenopausal women. Patients in the VEC group were younger and exhibited lower BMI. Comparing the clinicopathological outcomes between the groups the tumor size, presence of polyp, and time interval between diagnosis and surgery were similar. Endometrial intraepithelial neoplasia (EIN) and hyperplasia rates were similar between groups. The 5-y DFS and OS were also similar between groups.

Patients in the VEC group were younger. This aligns with recent studies indicating that patients with vanishing cancer are often younger (3). Notably, the mean BMI in the VEC group was also lower, raising questions about the interplay between obesity, estrogen production, and cancer progression. As we know type 1 EC is estrogen dependent and being overweight may contribute to the invasion rate of cancer by causing excessive estrogen secretion from adipose tissue (2). This may be the cause of lower BMI value in VEC group.

The results indicate impressive survival rates, with a 5-year OS of 97.5% and a DFS of 99.2%, highlighting the favorable prognostic outlook for early-stage EC when managed through appropriate surgical interventions. Importantly, no significant differences in DFS or OS were noted between the two types. A recent study reported similar survival with our study (7). The lack of significant differences in DFS or OS between two types suggests that the current treatment paradigms for both VEC and SEC may yield comparable outcomes, which could challenge existing notions regarding the aggressiveness or treatment needs of VEC.

Our findings support existing literature regarding the efficacy of lymph node dissection in enhancing staging accuracy as evidenced by most patients undergoing this procedure (8). The low incidence of adjuvant chemotherapy (5.4%) reinforces the common management approach for early-stage diseases, which typically involves surgical intervention as the primary strategy.

The similar rates of endometrial intraepithelial neoplasia (EIN) and hyperplasia between groups – ranging from 30% to 50% in hysterectomy specimens – suggest that hysterectomy may be warranted even in patients classified as having vanishing tumors. This is further supported by findings from another study reporting high rates of endometrial hyperplasia with atypia among VEC patients (76.2% endometrial hyperplasia with atypia, and 4.8% endometrial hyperplasia without atypia) (3).

This study is subject to several limitations inherent in retrospective designs, including biases in patient selection and limited generalizability due to the single institution setting. Furthermore, the small sample size of VEC patients limits the statistical power to derive broader conclusions. The absence of molecular analysis in many cases is another drawback.

To the best of our knowledge, this study demonstrates one of the largest cohorts with over six years of median follow-up for VEC, allowing for a comparative evaluation of clinicopathological characteristics and and survival outcomes between VEC and SEC.

In conclusion, while vanishing endometrial cancer remains a rare entity, it necessitates hysterectomy due to the high incidence of hyperplasia or EIN in the surgical specimens. Furthermore, the absence of EC in these specimens may lead both clinicians and patients to underestimate the disease, potentially resulting in undertreatment or insufficient follow-up.

Conflict Of Interest

The authors declare there is no conflicts of interest.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Evaluation of perioperative outcomes of hyperthermic intraperitoneal chemotherapy treatment in ovarian cancer patients undergoing interval cytoreduction: a retrospective analysis

Interval sitoredüksiyon uygulanan over kanseri hastalarında hipertermik intraperitoneal kemoterapi tedavisinin perioperatif sonuçlarının retrospektif değerlendirilmesi

Selçuk ERKILINÇ[1], Sena ÖZCAN[2], Ayşe Betül ÖZTÜRK[3], Serhan Can İŞCAN[4], Ufuk ATLIHAN[5], Can ATA[1], Hüseyin Aytuğ AVŞAR[6], Tevfik Berk BİLDACI[1], İlker ÇAKIR[1]

[1]İzmir Democracy University School of Medicine, Buca Seyfi Demirsoy Education and Research Hospital, Department of Gynecologic Oncology, İzmir, Türkiye
[2]Ministry of Health Sarıgöl Public Hospital, Department of Obstetrics and Gynecology, Manisa, Türkiye
[3]Ministry of Health Muş Public Hospital, Department of Obstetrics and Gynecology, Muş Türkiye
[4]Isparta City Hospital, Isparta, Türkiye
[5]Manisa Merkezefendi Public Hospital, Department of Obstetrics and Gynecology, Manisa, Türkiye
[6]İzmir Tınaztepe University, School of Medicine,Departments of Gynecology and Obstetrics İzmir, Türkiye

ABSTRACT

Aims: To evaluate the intraoperative and postoperative outcomes of the patients underwent interval cytoreduction and hypertermic intraperitoneal chemotherapy

Materials and Methods: This retrospective study included 23 patients who underwent cytoreductive surgery with HIPEC for high-grade serous ovarian cancer between December 2021 and September 2023 at our gynecologic oncology unit. HIPEC was performed using cisplatin at a dose of 100 mg/m², with continuous perfusion at 42°C for 90 minutes. Clinical characteristics, including age, comorbidities, preoperative CA-125 levels, and surgical details, were collected. Intraoperative parameters such as the extent of resection, anesthesia duration, transfusions, and urine output were analyzed. Postoperative complications, including acute renal insufficiency (ARI), were evaluated using daily creatinine measurements. Statistical analyses were conducted using SPSS 25, with continuous variables presented as mean ± standard deviation or median (range).

Results: The mean age of patients was 61 ± 10 years, and 78.6% were postmenopausal. The median gravida and parity were 3 (range: 2–7). 69.6% had ascites, with a median volume of 1000 mL (0–3000 mL). The median peritoneal carcinomatosis index (PCI) score was 14 (6–28). Neoadjuvant chemotherapy was administered to 91.3% of patients, with a median interval of 31.6 ± 4.6 days between NACT and surgery. The most common procedures performed included omentectomy (100%), colonic resection (13%), small bowel resection (8.7%), and splenectomy (21.7%). The median operation time was 316 minutes, and the median intraoperative bleeding was 400 mL (300–1000 mL). The median hospital stay was 10 days (5–19). Acute renal insufficiency (ARI) occurred in 21% of patients, while other complications included ileus (13%), wound infection (17%), and atelectasis (21%). Median creatinine levels were 0.8 mg/dL on Postoperative Day 1, 1.1 mg/dL on Postoperative Day 2, and 0.9 mg/dL on Postoperative Day 3, indicating a transient postoperative rise in renal dysfunction. All patients who required renal replacement therapy had received cisplatin-based HIPEC at a dose of 100 mg/m². The median urine output during HIPEC was 400 mL, suggesting the need for close renal monitoring.

Conclusion: Cytoreductive surgery with HIPEC in ovarian cancer is a feasible option for advanced ovarian cancer with acceptable renal and surgical morbidity

Keywords: Ovarian cancer, interval cytoreduction, hyperthermic intraperitoneal chemotherapy

ÖZ

Amaç: Intetval sitoredüksiyon ve hipertermik intraperitoneal kemoterapi (HIPEC) uygulanan hastaların intraoperatif ve postoperatif sonuçlarını değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Aralık 2021 ile Eylül 2023 tarihleri arasında jinekolojik onkoloji birimimizde yüksek dereceli seröz over kanseri nedeniyle sitoredüktif cerrahi ve HIPEC uygulanan 23 hasta dahil edildi. HIPEC, 100 mg/m² dozunda sisplatin ile 42°C'de 90 dakika boyunca sürekli perfüzyon şeklinde uygulandı. Hastaların klinik özellikleri (yaş, ek hastalıklar, preoperatif CA-125 seviyeleri ve cerrahi detaylar) kaydedildi. Yapılan cerrahi işlemler, anestezi süresi, kan transfüzyonu gereksinimi ve idrar çıkışı bilgilerine ulaşıldı. . Postoperatif komplikasyonlar, özellikle akut böbrek yetmezliği (ABY), günlük kreatinin ölçümleri ile değerlendirildi. İstatistiksel analizler SPSS 21 kullanılarak yapıldı; sürekli değişkenler ortalama ± standart sapma veya medyan (min–maks) olarak sunuldu.

Bulgular: Hastaların yaş ortalaması 61 ± 10 yıl olup, %78,6'sı postmenopozaldı. Medyan gravida ve parite sırasıyla 3 (2–7) idi. Hastaların %69,6'sında asit mevcuttu ve medyan hacmi 1000 mL (0–3000 mL) olarak ölçüldü. Medyan peritoneal karsinomatoz indeksi (PCI) 14 (6–28) idi. Neoadjuvan kemoterapi hastaların %91,3'üne uygulanmış olup, cerrahi ile neoadjuvan kemoterapi arasındaki medyan süre 31,6 ± 4,6 gündü. En sık uygulanan cerrahi işlemler omentektomi (%100), kolonik rezeksiyon (%13), ince bağırsak rezeksiyonu (%8,7) ve splenektomi (%21,7) idi. Medyan operasyon süresi 316 dakika, medyan intraoperatif kanama miktarı ise 400 mL (300–1000 mL) olarak kaydedildi. Postoperatif olarak, medyan hastanede kalış süresi 10 gündü (5–19). Akut böbrek yetmezliği (ABY) %21 oranında görülürken, diğer komplikasyonlar arasında ileus (%13), yara enfeksiyonu (%17) ve atelektazi (%21) yer aldı. Medyan kreatinin seviyeleri postoperatif 1. günde 0,8 mg/dL, 2. günde 1,1 mg/dL ve 3. günde 0,9 mg/dL olarak ölçüldü ve postoperatif dönemde geçici bir böbrek fonksiyon bozukluğunu gösterdi. Renal replasman tedavisi gerektiren tüm hastalar 100 mg/m² dozunda sisplatin bazlı HIPEC almıştı. Medyan intraoperatif idrar çıkışı 400 mL olup, bu durum böbrek fonksiyonlarının yakından izlenmesi gerekliliğini göstermektedir.

Sonuç: Over kanseri tedavisinde interval sitoredüktif cerrahi ve eş zamanlı sıcak intraperitoneal kemoterapi kabul edilebilir renal ve cerrahi morbidite ile ilişkili bir tedavi yöntemidir.

Anahtar Kelimeler: Over kanseri, sıcak intraperitoneal kemoterapi, interval sitoredüksiyon

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Sorumlu Yazar/Corresponding Author: Selçuk ERKILINÇ, Dokuz Eylül Mahallesi, Ata Caddesi, 35. Sokak Evleri Ulukent Menemen İzmir, Türkiye
E-mail: selcukerkilinc@hotmail.com

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INTRODUCTION

Ovarian cancer is one of the gynecological malignancies that is typically diagnosed at an advanced stage (1). The main reasons for the lack of early diagnosis are the absence of an effective screening method and the asymptomatic nature of the disease in its early stages (2). As with all cancer types, treatment becomes more complicated as the disease progresses. Given that the majority of ovarian cancer cases are diagnosed at an advanced stage, a multimodal treatment approach is often required rather than a single treatment modality (3).

For many years, the cornerstone of ovarian cancer treatment has been surgery aimed at achieving optimal cytoreduction, which remains the most effective therapeutic intervention (4). The maximum benefit of surgical treatment can only be achieved when optimal cytoreduction is accomplished. In cases where optimal surgery cannot be performed, the use of neoadjuvant chemotherapy followed by interval cytoreduction has been shown to provide benefit if a good response is achieved with chemotherapy (4, 5).

Hyperthermic intraperitoneal chemotherapy (HIPEC) is utilized in ovarian cancer to enhance the efficacy of chemotherapy by targeting tumor cells on the peritoneal surfaces with higher drug concentrations (6). Although the benefit of HIPEC has been demonstrated in some studies, particularly in interval cytoreduction following neoadjuvant chemotherapy, many studies have failed to show a significant advantage (7). Complications associated with HIPEC, such as nephrotoxicity and the risk of intestinal anastomotic leakage, are significant concerns that need to be addressed.Current literature on HIPEC provides no definitive recommendations, emphasizing the need for further research to establish its role in ovarian cancer treatment (8).

In light of this information, the aim of our study was to evaluate the intraoperative and postoperative outcomes associated with HIPEC in patients who underwent interval cytoreduction for ovarian cancer.

MATERIAL AND METHOD

This retrospective study was conducted after obtaining institutional review board approval. Data from patients treated for ovarian cancer between 2021 and 2023 were reviewed. Patients with histopathologically confirmed high-grade serous ovarian cancer were included, while those with mucinous carcinoma, pseudomyxoma peritonei, or non-gynecologic peritoneal carcinomatosis were excluded from the analysis. Patient records were retrieved from the hospital database. All samples were evaluated by experienced gynecopathologists to confirm the diagnosis.

Patients who underwent primary cytoreduction were excluded from the study. For patients deemed unsuitable for primary cytoreduction three cycles of platinum-based neoadjuvant chemotherapy were administered. Chemotherapy response was assessed using imaging modalities and CA-125 tumor marker levels. Patients who showed no response to chemotherapy were considered inoperable and continued with systemic chemotherapy and excluded from the study. Conversely, patients with a favorable chemotherapy response underwent interval cytoreduction surgery within 20 to 30 days after completing the three chemotherapy cycles included to the study.

All interval cytoreduction procedures began with an exploratory laparotomy via a midline xiphoid-to-pubic incision. Surgical exploration was performed to assess the extent of disease, and any patient with tumor involvement of the small intestine root, pancreatic head, or residual tumor at the celiac trunk level following chemotherapy was not subjected to further surgical resection. For all other patients, the procedure commenced with a parietal peritonectomy. The parietal peritoneum was separated extraperitoneally from the fascia transversalis. The liver and spleen were mobilized to allow diaphragmatic peritonectomy. Parietal peritonectomy was extended caudally, and in cases with tumor involvement of the pelvic peritoneum, uterus, adnexa, or rectosigmoid colon, en bloc resection was performed, including the affected segment of the colon. In cases where tumor implants were detected on the small intestine mesentery, visceral peritonectomy was performed. When intestinal resections were performed, intestinal anastomoses were routinely carried out, even when HIPEC was planned.

Four chemotherapy infusion catheters and a temperature probe were inserted into the abdominal cavity. HIPEC was administered after the closure of all abdominal layers to ensure a contained perfusion environment. Cisplatin was used at a dose of 100 mg/m², diluted in 3000-4000 mL of isotonic saline solution. The procedure was performed using the Belmont Hyperthermic Intraperitoneal Perfusion System (Belmont Instrument Corporation, Billerica, MA, USA), which maintained the inflow temperature of the perfusate at 42°C through afferent ports. The HIPEC procedure was performed for 90 minutes, with urine output closely monitored throughout the process to assess renal function and fluid balance.

Comprehensive data were collected from the hospital records and demographic characteristics including age, gravida, parity, menopausal status, and body mass index, comorbidities, pre-HIPEC

CA-125 levels, the interval between neoadjuvant chemotherapy and interval cytoreduction, ECOG performance score, ASA score, presence and volume of ascites, details of surgical procedures including colon or small bowel resections, number of anastomoses, omentectomy, splenectomy, and lymphadenectomy), intraoperative parameters including duration of surgery and anesthesia, estimated blood loss, and transfusion requirements), and postoperative outcomes including hospital stay, daily creatinine monitoring, and complications.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) or median (range), depending on the data distribution, which was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequency (percentage).

RESULTS

The study included a total of 23 patients with a mean age of 61±10 years. The median gravida and parity values were 3 (2-7). Among the participants, 78.6% were postmenopausal, with a median menopausal age of 51 years. The median height and weight of the patients were 160 cm (153-170) and 79 kg (42-114), respectively, with a median BMI of 30 (17-45) Table 1 showed patients characteristics of the patients that underwent cytoresuctive surgery and HIPEC.

At least one of the comorbidities including diabetes (30.4%) and hypertension (26%) was present. One patient (2.7%) had a history of nephrolithiasis, and one patient (2.7%) had a history of breast cancer. The median preoperative CA-125 level was 824 (26-10,000). Neoadjuvant chemotherapy was administered to 91.3% of the patients, with a median interval of 31.6±4.6 days between NACT and surgery. The majority of patients (91.3%) showed a partial response, while 8.7% had a complete response. Preoperative diagnosis was established by tru-cut biopsy (30.4%), laparoscopic biopsy (21.7%), or other methods (21.6%) (Table 1).

Ascites was present in 69.6% (n:16) of patients, with a median volume of 1000 mL (0-3000 mL). The median peritoneal carcinomatosis index (PCI) score was 14 (6-28). Colonic resection was performed in 13%, small bowel resection in 8.7%, and anastomosis in 13% of the patients. Appendectomy was required in 47.9%, while omentectomy was performed in all patients (100%). Splenectomy was required in 21.7% of the patients. The median anesthesia duration was 406 minutes (275-646), and the median operation time was 316 minutes (185-556). The median intraoperative blood loss was 400 mL (300-1000), and the median transfusion of red blood cells (RBC) and fresh frozen plasma (FFP) was 2 units (0-4) each. Table 2 showed intraoperative characteristics of the patients.

Table 1. Clinical and Demographic Characteriscs of Patient that undervent Cytoreduction and HIPEC

Variable	Data
Age	61±10
Gravida	3 (2-7)
Parity	3 (2-7)
Menapause	
Premenaposal	3 (22,4%)
Postmenaposal	11 (78,6%)
Manaposal age	51 (4-61)
Height	160 (153-170)
Weight	79 (42-114)
BMI	30 (17-45)
Comorbidity	
None	9 (24.3%)
Yes	14 (37.8%)
Comorbidities	
Nefrolithiasis	1 (2.7%)
Diabetes	7 (30.4%)
Hypertension	6 (26%)
Breast Cancer	1 (2.7%)
Ca 125	824 (26-10000)
Diagnostic Laparoscopy	
No	14 (60.9%)
Yes	9 (24.3%)
Preoperative Diagnosis	
Tru-cut biopsy	7 (30,4%)
Laparoscopic biopsy	5 (21,7%)
Other	8 (21.6%)
Neoadjuvant Chemotherapy	
No	2 (8.7%)
Yes	21 (91.3%)
Time between NACT and Surgery	31.6±4.6
Response to NACT	
Partial response	21 (91,3%)
Total response	2 (8.7%)
ECOG Perfomance Score	
1	15 (65.2%)
2	8 (34.8%)
ASA Score	
1	3 (13%)
2	18 (91.3%)
3	3 (8.7%)

Postoperative pathological analysis revealed that 78.6% of the patients underwent lymphadenectomy due to palpable lymph nodes. The majority of tumors were grade 3 (91.3%), and the median number of resected pelvic and paraaortic lymph nodes was 16 (0-40) and 19 (0-37), respectively. Metastasis was detected in 0-7 pelvic lymph nodes and 0-10 paraaortic lymph nodes. The median hospital stay was 10 days (5-19) (Table 3).

Table 2. Intraoperative findings

Variable	Data
Ascites	
None	7 (30.4%)
Yes	16 (69.6%)
The amount of ascites	1000 (0-3000)
PCI Score	14 (6-28)
Colonic resection	
None	20 (87%)
Yes	3 (13%)
Small Bowel Resection	
None	21 (91.3%)
Yes	2 (8.7%)
Anastomosis	
None	20 (87%)
Yes	3 (13%)
Number of Anastomosis	
1	2 (66%)
2	1 (33%)
Appendicectomy	
None	12 (52.1%)
Yes	11 (47.9%)
Diaphragma stripping	14 (100%)
Torocal tube placement	-
Omentectomy	23 (100%)
Splenectomy	
None	18 (78.3)
Yes	5 (21.7%)
Anesthesia Time	406 (275-646)
Operation Time	316 (185-556)
Transfusion of RBC	2 (0-4)
Transfusion of TDP	2 (0-4)
Urine output during HIPEC	400 (300-1100)
Bleeding	400 (300-1000)

Postoperative complications were observed in several patients. The most common complications included acute renal insufficiency (21%), atelectasis (21%), and wound infection (17%). Ileus occurred in 13% of patients, while intestinal perforation, deep venous thrombosis, acute respiratory distress syndrome (ARDS), and myocardial infarction were each observed in 4.3% of cases (Table 3).

Figure 1 showed the trends in creatinine levels over time, depicting median, minimum, and maximum values at different time points.

DISCUSSION

Our study investigated intraoperative and postoperative characteristics of the ovarian cancer patients that underwent cytoreductive surgery and HIPEC. The fact that morbidities associated with HIPEC do not have long-term adverse effects and

Table 3. Postoperative pathological data of patients that underwent Cytoraduction and HIPEC aa

Variable	Data
Lympadenectomy	
None	5 (21,4%)
Palpable	19 (78,6%)
Grade	
2	2 (8.7%)
3	21(91.3%)
Pelvic Lymph node	16 (0-40)
Paraaortic Lymph node	19 (0-37)
Pelvic lymph nod metastasis	0 (0-7)
Paraaortic Lymph node metastasis	0 (0-10)
Hospital Stay	10 (5-19)
Complications	
Intestinal perforation	1 (4.3%)
Ileus	3 (13%)
Wound Infection	4 (17%)
Deep venous thrombosis	1 (4.3%)
Acute renal Insufficiency	5 (21%)
Atelektasis	5 (21%)
ARDS	1 (4.3%)
Myocardial Infarctus	1 (4.3)

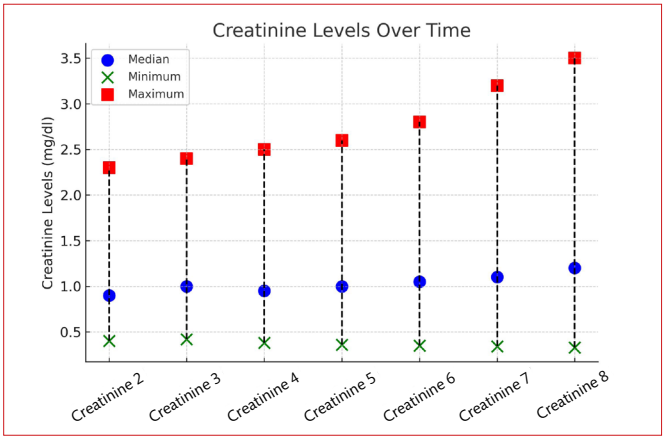

Figure 1. Trends in creatinine levels over time

that most of them are reversible in a short time may influence the decision-making process in favor of offering this treatment to the patients underwent inteval cytoreduction.

Several studies have evaluated the efficacy and safety of HIPEC in ovarian cance and reported mixed results. The OVHIPEC-1 trial demonstrated an improvement in both progression-free and overall survival when HIPEC was added to interval cytoreduction and and complete resection was achieved (9). On the other hand, following randomized studies, including the work by Lim et al., did not confirm a survival benefit when HIPEC was used either in the primary or interval setting (10). Furthermore, a phase II study by Zivanovic et

al. evaluating HIPEC with carboplatin in recurrent ovarian cancer failed to demonstrate an improvement in overall survival compared to surgery alone (11). The ongoing OVHIPEC-2 trial may help clarify the role of HIPEC in the upfront setting. As our study included only the patients underwent interval cytoreduction followed by neoadjuvant chemotherapy the application of the procedure is correlated with the usage of HIPEC reported in the literature.

A systematic review by Chiva et al. reported grade 3–4 complications in 19% of primary cases and 25% of recurrent cases, with mortality rates ranging from 0% to 7% (12). Similarly, a meta-analysis by Huo et al. found that mortality after HIPEC was 1.8%, comparable to our findings(13). Although we did not report any mortality this may be related with limited number of patients eligible for the study. Another meta-analysis by Bouchard-Fortier et al. showed that primary surgery plus HIPEC resulted in grade 3–4 complications in 34% of cases and an 8% rate of reoperation (14). These findings align with existing literature that reports common complications such as acute renal insufficiency, atelectasis, and wound infections, with similar incidence rates.

The variation in results across these studies can be attributed to differences in patient selection, chemotherapy regimens, and surgical expertise. Some centers have reported better outcomes with strict patient selection criteria, particularly excluding patients with extensive disease that cannot be optimally debulked. Additionally, the choice of chemotherapeutic agents, HIPEC duration, and temperature settings have varied significantly among studies, contributing to inconsistent findings (15). In our study we applied a standart HIPEC regimen whic was never the time below 90 minutes indicatig more acccurate results associated with treatment. On the other hand there is a tendency among the surgeons to cease the HIPEC before the standart time to avoid the complications. The studies reporting lesser complications may have used lower dose and decreased time of application of the HIPEC treatment.

HIPEC is associated with significant perioperative morbidity due to the extent of surgical resection required to achieve optimal cytoreduction and the cytotoxic effects of intraperitoneal chemotherapy. Previous studies have reported median PCI scores ranging from 10 to 20, reflecting extensive peritoneal disease (16, 17). The presence of ascites in up to 70% of patients and the frequent need for additional procedures such as colonic resection (10–25%), small bowel resection (5–15%), and splenectomy (15–30%) have been highlighted in various studies, demonstrating the aggressive nature of surgery required in HIPEC cases(17).

Postoperative complications such as ileus and intestinal perforation are of particular concern, as prior research has indicated a higher risk of anastomotic leaks when HIPEC is performed following bowel resection . The CHIPOVAC trial, which used oxaliplatin for HIPEC, had to be closed prematurely due to excessive rates of hemoperitoneum (18). Additionally, renal toxicity is a well-recognized adverse effect of HIPEC, particularly when cisplatin is used. Despite the absence of sodium thiosulfate use in our study, nephrotoxicity rates remained low, consistent with findings from studies that suggest optimized perioperative hydration protocols may help mitigate this risk (19). Other studies have reported nephrotoxicity rates as high as 48% in some cohorts, yet our findings align with research indicating that renal function can be preserved with adequate intraoperative management.

Furthermore, ICU admission rates have varied across studies, ranging from 20% to 89%, depending on the perioperative management strategies used (17, 20). This variability suggests that optimization of perioperative care, including fluid management and early mobilization, may help reduce ICU stays and postoperative morbidity.

Given the high rates of complications and the lack of consistent survival benefit in randomized trials, HIPEC should be considered cautiously and offered within clinical trials or high-volume centers with expertise in ovarian cancer surgery. The Enhanced Recovery After Surgery (ERAS) guidelines for cytoreductive surgery recommend meticulous perioperative management to mitigate morbidity, emphasizing fluid management, early mobilization, and nutritional support (21). The potential benefits of HIPEC must be weighed against its risks, particularly in patients with pre-existing comorbidities such as renal dysfunction (22).

Our findings align with the retrospective analysis by Liesenfeld et al., which identified cisplatin-based HIPEC regimens as a significant contributor to HIPEC-associated nephrotoxicity. Their study reported an ARI incidence of 31.8%, a rate comparable to our findings (23). Notably, our results also indicate a marked increase in creatinine levels post-HIPEC, with the most substantial rise observed on postoperative day 2, consistent with previous reports (24). The preclinical mouse model presented by Liesenfeld et al. demonstrated that cisplatin, rather than hyperthermia, was the primary driver of ARI, supporting the hypothesis that nephrotoxicity in HIPEC is largely chemotherapy-induced rather than a direct consequence of hyperthermic perfusion (23)

Importantly, all patients who required renal replacement therapy had received cisplatin-based HIPEC, further emphasizing its nephrotoxic potential (23). The high incidence of acute renal insufficiency may be explained with the dose that we administered to the patients was standart of 100 mg/m². Patient selection is

crucial when considering HIPEC, and its use should be restricted to those likely to achieve complete cytoreduction. Some studies have suggested that HIPEC may be more beneficial in patients with a low tumor burden and optimal resection, whereas those with extensive peritoneal involvement may not derive significant survival advantages (25). In addition, although recent trials have suggested that genetic and molecular profiling of ovarian cancer may provide insights into which patients are most likely to benefit from HIPEC, our study did not include genetic testing, preventing any conclusions regarding the interaction between HIPEC efficacy and molecular tumor characteristics (24).

The retrospective nature of our study introduces potential selection bias. Additionally, our sample size is relatively small, limiting the generalizability of our findings. Another limitation is the heterogeneity in chemotherapy regimens and patient characteristics, which may affect outcomes. Future prospective studies with standardized HIPEC protocols and robust quality-of-life assessments are needed to determine whether the benefits of HIPEC outweigh the risks in select patient populations.

Despite these limitations, our study contributes to the growing body of literature on HIPEC in ovarian cancer by highlighting its intraoperative and postoperative challenges. Moving forward, ongoing randomized trials such as OVHIPEC-2 and CHIPPI-1808 will be crucial in refining the role of HIPEC in ovarian cancer management (26). Furthermore, long-term follow-up studies will help assess the impact of HIPEC on disease recurrence and patient quality of life, ultimately guiding future treatment protocols.

CONCLUSION

HIPEC treatment, although leading to temporary renal morbidity in patients undergoing interval cytoreduction, is a feasible treatment option that can be performed without causing life-threatening complications.

Author Contributions

Study concept and design: S.E., C.A. Data collection: S.Ö., A.B.Ö., S.İ., U.A. Statistical analysis and interpretation: İ.Ç., S.E. Manuscript drafting: H.A.A., T.B.B. Manuscript review and editing: S.E., C.A. All authors have read and approved the final version of the manuscript.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to the authorship and publication of this article.

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TEZ ÖZETİ / THESIS ABSTRACT

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Cytoreductive surgery in advanced endometrial cancer: the impact of optimal cytoreduction and adjuvant treatment method

İleri evre endometrium karsinomunda sitoreduktif cerrahinin yeri

Refaettin ŞAHİN[1], Yusuf YILDIRIM[2]

[1]Şırnak Devlet Hastanesi, Şırnak, Türkiye
[2]Özel Klinik, İzmir, Türkiye

ABSTRACT

Aim: To identify important prognostic variables and evaluate the contribution of cytoreductive surgery on survival in advanced endometrial carcinoma.

Materials and Methods: The files of patients with endometrial cancer admitted to Izmir Ege Maternity and Gynecology Training and Research Hospital between January 1995 and December 2009 were reviewed. Sixty-one patients with advanced stage (Stage 3 and Stage 4) endometrial carcinoma were included in the study. Important prognostic variables in advanced endometrial carcinoma were determined and the contribution of cytoreductive surgery on survival was evaluated. The staging was performed according to the FIGO surgical staging system.

Results: The study included 61 patients. All patients underwent primary cytoreduction. The mean age of the patients at the time of diagnosis was 58 years. 18% of the patients were premenopausal and 82% were postmenopausal. The histologic types were endometrioid (78.7%), serous (11.5%), adenosquamous (6.6%), clear cell (1.6%), and epithelial (1.6%). Surgical staging revealed that the most common sites of metastasis were lymph node (52.4%), pelvis (45.9%), omentum (8.1%), upper abdomen (8.1%), and extra-abdominal (8.1%). The endometrioid type was found to have a longer survival than other histologic types. The mean survival was 119 ± 10 months in patients with optimal cytoreduction and 22 ± 6 months in patients with suboptimal cytoreduction.

Conclusion: In our study, optimal cytoreduction was defined as residual disease with a tumor size of 1 cm or less. Accordingly, there is a significant correlation between optimal cytoreduction and survival.

Keywords: Endometrial carcinoma, advanced stage, cytoreductive surgery

ÖZ

Amaç: İleri evre endometrium karsinomunda önemli prognostik değişkenleri belirlemek ve sitoreduktif cerrahinin sağ kalım üzerine katkısını değerlendirmektir.

Gereç ve Yöntemler: Ocak 1995 – Aralık 2009 yılları arasında İzmir Tepecik Doğumevi'ne başvuran endometrium kanserli olgulara ait dosyalar incelendi. İleri evre (Evre 3 ve Evre 4) endometrium kanseri olan 61 olgu çalışmaya dahil edildi. İleri evre endometrium karsinomunda önemli prognostik değişkenler belirlenerek, sitoreduktif cerrahinin sağ kalım üzerine olan katkısı değerlendirildi. Evreleme FIGO cerrahi evreleme sistemine göre yapıldı.

Bulgular: Çalışmaya 61 hasta dahil edildi. Tüm hastalara primer sitoredüksiyon uygulandı. Hastaların tanı anındaki yaş ortalaması 58'di. Hastaların %18,03'ü premenopozal, %81,07'si postmenopozal dönemde olduğu görüldü. Çalışmada histolojik tipler; endometrioid (%78,7), seröz (%11,5), adenoskuamoz (%6,6), clear cell (%1,6) epitelial (%1,6) olarak saptandı. Cerrahi evreleme sonucunda, en sık metastaz alanları lenf nodu (%52,4),pelvis (%45,9), omentum (%8,1), üst abdomen (%8,1), ekstra abdominal (%8,1) olarak saptandı. Endometrioid tipin diğer histolojik tiplere daha uzun bir sağ kalımı olduğu tespit edilldi. Optimal sitoredüksiyon uygulanan hastalarda ortalama sağ kalım 119+10 ay, suboptimal sitoredüksiyon uygulanan hastalarda 22+6 ay olarak bulundu. Optimal sitoredüksiyon, hastalara 97 aylık bir sağ kalım avantajı sağlamaktadır. Ayrıca; 24 ay sonunda optimal sitoredüksiyon uygulananhastaların %72'si hayatta iken, suboptimal sitoredüksiyon uygulanan hastaların %22'si hayatta kaldı.

Sonuç: Çalışmamızda optimal sitoredüksiyon; tümör boyutu 1 cm ve altında rezidüel hastalık olarak kabul edilmiştir. Buna göre; optimal sitoredüksiyon ile sağ kalım arasında anlamı bir bağlantı vardır. Bu bilgi literatür bilgisiyle uyumlu olarak bulunmuştur. Geniş vaka serileri ile yapılacak çalışmalarla bu konu hakkında daha net fikirler elde edilebilir.

Anahtar Kelimeler: Endometrium karsinom, ileri evre, sitoreduktif cerrahi

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Sorumlu Yazar/Corresponding Author: Refaettin ŞAHIN, Şırnak Devlet Hastanesi, Bahçelievler, Nucan Caddesi No:34, 73000 Şırnak/Merkez, Türkiye
E-mail: refaettin_sahin@yahoo.com

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INTRODUCTION

Gynecologic cancers constitute approximately 13% of all cancers seen in women.[1] In developed countries, endometrial cancer is the most common cancer in the female genital system. Every year, 142000 women are diagnosed worldwide and 42000 women die from this disease.[2] Endometrial cancer is the fourth most common cancer in women after breast, bowel, and lung cancer. The average incidence is 24.7 per 100,000 women. The cumulative risk of endometrial cancer in a 75-year-old woman is 1.7%. Despite its high incidence and the lack of an effective screening test, it ranks low among the causes of death due to its early symptoms and treatment options and is the 8th most common cause of cancer-related deaths.[3] According to data from the Ministry of Health, it ranks 2nd among malignancies of the female genital system in Turkey.[4]

According to histologic features, endometrium cancer is divided into type 1 and type 2. Type 1 endometrial carcinoma is seen in 80% of cases. They are endometrioid adenocarcinomas (or adenosquamous, mucinous, villoglandular) showing good or moderate differentiation and limited to the uterine corpus at the time of diagnosis. Type 2 endometrial carcinoma is seen in 15-20% of cases. They are high-grade carcinomas such as clear cell and serous carcinomas showing nuclear atypia. These tumors usually invade the myometrium and spread outside the uterus during hysterectomy. Since the prognosis of the second group is worse, the pathologist who makes the diagnosis becomes more important in planning the patient's treatment.

Endometrial carcinoma is a cancer that has been surgically staged since 1988 according to the decision of the International Federation of Gynecology and Obstetrics (FIGO). The conventional surgical approach includes midline abdominal incision followed by peritoneal washing and cytology collection, total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy in selected high-risk cases, pelvic and paraaortic lymphadenectomy. [5]

The incidence of endometrial carcinoma is increasing and it is rapidly climbing up the list of gynecological cancers. For this reason, serious research is being carried out to find out the risk factors, screening methods for early diagnosis, factors affecting prognosis, and the most effective treatment methods on life expectancy. Although in the vast majority of patients, the carcinoma is confined to the uterus, in approximately 20% the tumor metastasises to pelvic lymph nodes and more distant organs. The surgical management of early-stage endometrial cancer has been clearly defined, but metastatic and recurrent disease has a poor response to current treatment regimens and the optimal management of these patients is still to be determined.

Advanced endometrial cancer poses a problem from a clinical point of view. The reason for this is the lack of consensus on the most effective treatment method and the poor survival data of the disease to date. Especially stage 3 and stage 4 patients are responsible for 50% of endometrial cancer-related deaths. In stage 4 disease, 5-year survival is around 10-20%.[6,7] Therefore, the role of radical surgery in the management of patients with advanced endometrial carcinoma is increasing, especially in the management of patients who are expected to benefit from adjuvant radiotherapy or chemotherapy.

This study aimed to determine important prognostic variables in advanced endometrial carcinoma and to evaluate the contribution of cytoreductive surgery on survival.

MATERIAL AND METHODS

In this retrospective study, the files of patients with endometrial cancer admitted to Izmir Ege Maternity and Gynecology Training and Research Hospital between January 1995 and December 2009 were analyzed. Seventy-four patients with advanced stage (Stage 3 and Stage 4) endometrial cancer were identified. Due to incomplete files, 13 cases were excluded from the study and 61 cases were included in the study. All patients underwent primary cytoreduction.

The contribution of cytoreductive surgery on survival in advanced endometrial carcinoma was evaluated by determining important prognostic variables. The staging was performed according to the FIGO surgical staging system. SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for statistical analysis. All data are summarized in tables. Study

In addition to descriptive statistical methods (mean, standard deviation, percentage, minimum, and maximum value), the log-rank method was used for univariate analyses and the Cox proportional hazards regression test for multivariate analyses for intra- and intergroup comparisons of quantitative data. Pearson's chi-square and Fisher's chi-square tests were used to compare qualitative data. The results were evaluated at a 95% confidence interval and significance level $p<0.05$.

RESULTS

The age distribution of the patients at the time of diagnosis was between 32 and 77 years with a mean of 58 years. 77% of the

patients were younger than 65 years and 23% were older than 65 years. 18.03% of the patients were premenopausal and 81.07% were postmenopausal. The histologic types were endometrioid (78.7%), serous (11.5%), adenosquamous (6.6%), clear cell (1.6%), and not specified (malignant epithelial) (1.6%), respectively. Pathology results were grade 3 (poorly differentiated) in 14 cases, grade 2 (moderately differentiated) in 28 cases, and grade 1 (well differentiated) in 11 cases. In 8 cases, the reason for not specifying grade was serous and clear cell histology. When the cases were evaluated according to their stages; Stage 3a (n=20), Stage 3b (n=2), Stage 3c (n=35), Stage 4a (n=1), and Stage 4b (n=3) cases were detected.

All 61 patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, staging surgery, and maximal cytoreduction by explorative laparotomy. Hysterectomy was performed in 100% of the patients (61/61). 39 patients underwent type 1 hysterectomy, 6 patients underwent type 2 hysterectomy, and 16 patients underwent type 3 hysterectomy. 20 patients underwent omentectomy, 54 patients underwent lymph node dissection and 12 patients underwent appendectomy. Optimal cytoreduction was defined as a residual tumoural disease with a maximum diameter of less than 1 cm. Optimal cytoreduction was performed in 86.9% and suboptimal cytoreduction in 13.1% of the patients. Abdominal wash cytology revealed 72.1% benign cytology, 24.6% malignant cytology, and 3.3% suspicious cytology. Abdominal wash cytology was not included in survival analyses because it has no prognostic significance in the 2009 FIGO staging system. Demographic and disease-related characteristics of the research sample are summarized in Table 1.

A total of 43 patients (41%) received postoperative chemotherapy. These patients received cisplatin alone or a combination of cisplatin with doxorubicin, cyclophosphamide, and paclitaxel. Radiotherapy was given additionally in 36 of these patients. 18 patients received radiotherapy only. Radiotherapy was administered as whole abdomen radiotherapy or brachytherapy.

In the calculation of survival for all patients who participated in the study, median survival could not be calculated because there were not enough patients in the ex-group, and mean survival was calculated instead. The mean survival of all patients participating in the study was 111 ± 10 months. When the patients were evaluated

Table 1. Demographic and disease-related characteristics of the study sample

	N	%
Age (mean, yrs)	58 (range 32-77)	
Menopausal status		
Pre-menopausal	11	18.0%
Post-menopausal	50	82.0%
Hystologic Types		
Endometrioid	48	78.7%
Serous	7	11.5%
Adenosquamous	4	6.6%
Clear Cell	1	1.6%
Not specified (malignant epithelial)	1	1.6%
Grade		
Low grade (G1)	11	18.0%
Intermediate grade (G2)	28	45.9%
High grade (G3)	22	36.1%
Disease Site (Anatomic localization)		
Lymph node	32	52.4
Pelvis	28	45.9
Omentum	5	8.1
Upper abdomen	5	8.1
Extra-abdominal	5	8.1
Peritoneal cytology (fluid/washing)		
Benign	44	72.1%
Malignant	15	24.6%

according to age groups, although patients younger than 65 years had longer survival, there was no statistically significant difference between them and patients older than 65 years (p=0.95). When the cases were evaluated according to histological subtypes, it was found that the endometrioid type had a longer survival than other histological types (p=0.001*). There was no statistically significant difference between tumor grade and survival. When stage 3 patients were compared within themselves, there was no significant difference in survival between the group with lymph node involvement and the group without lymph node involvement (p= 0.49).

Cases were compared in terms of residual disease volume and the mean survival was 119 ± 10 months in patients with optimal cytoreduction (1 cm or less residual tumor) and 22 ± 6 months in patients with suboptimal cytoreduction.This difference is statistically significant (p= 0.009*). It is seen that optimal cytoreduction provides a 97-month survival advantage to patients. Furthermore, 72% of patients with optimal cytoreduction were alive at 24 months, compared to 22% of patients with suboptimal cytoreduction. The procedures, surgical optimality and adjuvant treatment methods are summarized in Table 2.

When the cases were evaluated according to metastasis and disease extent; there was no statistical difference in survival between disease limited to the pelvis and disease spread outside the pelvis (p= 0.997). When Stage 3 cases were evaluated according to treatment modalities, it was observed that only chemotherapy or radiotherapy+chemotherapy combination had no significant contribution to survival. However, it was found that 18 patients who received radiotherapy alone had a survival of 141 ± 16 months and had a better survival than the group of patients who received chemotherapy alone 35 ± 14 months (p= 0.015*). However, there was no superiority to the radiotherapy+chemotherapy group.

Table 2. Procedures, surgical optimality and adjuvant treatment methods

	N	%
Procedures performed		
TAH-BSO	61*	100%
Omentectomy	20	32.8%
RPLND	54	88.5%
Appendectomy	12	19.7%
Rectosigmoid resection	1	1.6%
Visceral/Parietal peritonectomies**	5	8.2%
Surgical Optimality		
Optimal cytoreduction	53	86.9%
Suboptimal cytoreduction	8	13.1%
Perioperative Morbidity & Unintended Events		
Blood product transfusion	4	6.5%
Bladder injury	1	1.6%
Re-exploration due to hemorrhage	1	1.6%
Delayed (>72 hrs) ICU stay	1	1.6%
Deep venous thrombosis	1	1.6%
Atelectasis	1	1.6%
Wound infection (superficial)	2	3.2%
Urinary tract infection	1	1.6%
Adjuvant treatment		
Chemotherapy	7	11.5%
RT	18	29.5%
Chemo-RT***	36	59.0%

TAH-BSO: Total abdominal hysterectomy and bilateral salphingo-oophorectomy, RPLND: Retroperitoneal Lymph Node Dissection, ICU: Intensive care unit, RT: Radiotherapy
*: Two of which include Type 2 Hysterectomy
**: Pelvic, anterior abdominal wall, diaphragma
***: sequential or sandwitch medhod

DISCUSSION

Patients with advanced endometrial cancer constitute approximately 15-20% of all newly diagnosed patients, but more than half of all deaths due to endometrial cancer occur in this group. Prognostic variables and effective management strategies for patients in this group have not been determined until recently. In this study, the effect of residual disease volume on survival and other variables affecting survival in advanced endometrial cancer were analyzed.

To date, there are conflicting data in the literature about the effect of age on survival. Many researchers have found that age has no prognostic significance.[8,9] In a study by Pliskow et al. evaluating prognostic factors in 41 patients with advanced endometrial cancer, no significant association was found between age and survival.[9] However, in a study by Okuma et al. involving 111 patients with advanced endometrial cancer, survival was found to be longer in patients aged 60 years and younger.[10] Furthermore, Yutaka et al. evaluated the prognostic significance of cytoreductive surgery in 33 patients with stage 4 endometrial carcinoma and found that patients aged 70 years and younger had longer survival.[11] Similarly, in our study, survival was found to be longer in patients under 65 years of age, but it was not statistically significant.

Similar to previous studies, no significant correlation was shown between survival and tumor grade, and metastasis distribution in our study.[12] Bristow et al. performed cytoreductive surgery in 65 advanced endometrial carcinomas and published the results. In their study, the sites of metastasis were the pelvis (75.4%), omentum (49.2%), and retroperitoneal lymph node (38.5%), respectively. In our study, the most common sites of metastasis were the retroperitoneal lymph node (52.4%), pelvis (45.9%), and omentum (8.1%). Although there are proportional differences in other studies, the sites of metastasis are similar. [13]

No significant association was found between tumor histology and survival in previous studies. In the GOG study of 1203 patients in which McMeekin et al. investigated histological type and response to chemotherapy in advanced endometrial carcinoma, no difference was found between histological type and response to chemotherapy.[14] In their study, although survival was found to be shorter in patients with serous histology, it was not found to be statistically significant since this patient group constituted a small portion of the whole group. In a study conducted by Yutaka et al. in 33 patients with advanced-stage endometrial carcinoma, although a longer survival was found in patients with endometrioid histology, it was not statistically significant.[11] In our study, when tumor histology was evaluated independently of other factors, survival was found to be significantly higher in the patient group with endometrioid histology compared to the patient group with other histologies. The mean survival was 128 ± 11 months in the patient group with endometrioid histology and 24 ± 4 months in the patient group with other histologies. The association between endometrioid histology and prolonged survival persisted in multivariate analyses. It is possible that the fact that our patient group with endometrioid histology was more numerous than the patient group with other histologies may have led to this result.

There is no comprehensive study on the prognostic value of general conditions in endometrial cancer. Recent studies have shown a link between preoperative general condition and survival as an independent factor. These data suggest that patients who are healthier and have a higher performance scale tolerate extensive cytoreductive surgery better, resulting in optimal cytoreduction and postoperative adjuvant therapy. Since GOG performance was not evaluated in our hospital files, this parameter was not studied.

Confirming previous investigators, treatment modality could not be shown to contribute to survival as an independent variable in our multivariate analysis.[15] Marcus et al. compared the efficacy of whole abdominal radiotherapy with doxorubicin+cisplatin chemotherapy in 423 patients with advanced endometrial carcinoma treated with optimal cytoreduction and published their results (GOG 122). In their study, they found that chemotherapy had a longer disease-free period and a longer survival compared to radiotherapy. Barlin and Bristow performed a meta-analysis of 14 studies evaluating 672 patients with advanced primary and recurrent endometrial carcinoma who underwent cytoreduction and published their results. According to this meta-analysis, each 10% increase in the proportion of patients receiving postoperative radiotherapy leads to an 11-month increase in survival, while each 10% increase in the proportion of patients receiving chemotherapy leads to a 10.4-month decrease in survival.[16] Interestingly, in our study, when evaluated alone, the patient group receiving radiotherapy alone had an increased survival compared to the group receiving chemotherapy alone. When evaluated together with other variables (age, general condition, surgical status), radiotherapy loses this importance. This may be because younger, more functional patients tolerate aggressive surgery better. On the other hand, since the patients in our study who received chemotherapy had more widespread and extensive metastases, the choice of chemotherapy as treatment may lead to shorter survival. This idea is supported by the fact that stage 4 patients have a shorter survival.

In the GOG 28 and 48 studies, no difference was found between combination chemotherapy and single-agent chemotherapy in terms of survival. In the study of Thigpen et al. comparing

combination and single-agent chemotherapy in advanced endometrial carcinoma, no difference was found between single-agent doxorubicin and doxorubicin+cisplatin chemotherapy, but combination chemotherapy was found to be better in terms of disease-free period.[17] In our study, no such comparison was made between patients in the chemotherapy group. However, the contribution of postoperative treatment modality on survival in selected patients with advanced endometrial cancer may be better demonstrated in future studies.

Developing standard treatment protocols in advanced metastatic endometrial cancer is difficult due to the limited therapeutic efficacy of radiotherapy, chemotherapy, and hormonotherapy on large tumor burden.[18,19] Therefore, achieving minimal residual disease with cytoreductive surgery has greater therapeutic importance. In this study, tumor size was one of the two most important predictive factors for survival. This importance persists in multivariate analyses. Although young age and good general condition are associated with improved survival, the only prognostic factor that can be directly influenced by the surgeon is the amount of residual tumor. Extensive literature shows that less residual tumor burden is associated with better survival in advanced ovarian cancer treated with cytoreductive surgery.[20] However, the literature showing the importance of cytoreductive surgery in advanced endometrial cancer is more limited. Goff et al. performed cytoreductive surgery in 29 of 47 patients with advanced endometrial cancer and no bulky residual disease was left behind.[12] Unfortunately, the residual tumor size was not specified in cm in their study. Bristow et al. performed cytoreductive surgery in all 65 patients with advanced endometrial carcinoma and performed optimal cytoreduction in 36 and suboptimal cytoreduction in 29 of these patients. In their study, they accepted 1 cm as the limit for residual tumor size. In our study, all patients who participated in the study underwent cytoreductive surgery. Optimal cytoreduction was performed in 86.9% and suboptimal cytoreduction in 13.1% of the patients. Optimal cytoreduction was defined as residual tumor less than 1 cm was accepted as optimal cytoreduction. Survival of patients who underwent optimal cytoreduction was found to be significantly better than patients who underwent suboptimal cytoreduction.[13] This information clearly demonstrates the prognostic value of an optimal cytoreduction with minimal residual disease, although its real contribution to survival cannot be fully determined due to the type of surgery performed.

Greer and Hamberger applied postoperative whole abdomen radiotherapy to 31 patients with advanced endometrial cancer and found a 5-year survival rate of 70% in patients with residual tumors less than 2 cm. In our study, it was found to be similar to the literature with 63%. This study shows that adjuvant therapy in both stage 3 and stage 4 patients is much more successful in patients with minimal residual disease.[21] Chi et al. published the results of a study in which they performed cytoreductive surgery in 55 patients with advanced endometrial cancer. In this study, they found a significant correlation between the size of cytoreductive surgery and survival. In patients with tumors smaller than 2 cm, the median median survival was 31 months. This indicates that optimal cytoreduction patients who underwent suboptimal cytoreduction had a longer survival compared to those who underwent suboptimal cytoreduction (median survival 12 months).[8]

In a study conducted by Ayhan et al. in 37 patients with advanced endometrial carcinoma, median survival was 25 months in patients with optimal cytoreduction and 10 months in the suboptimal group. The median survival was 48 months in patients with no remaining microscopic tumor tissue. The majority of the patients consisted of endometrioid adenocarcinoma. In univariate analyses, extra abdominal metastasis, suboptimal cytoreduction, macroscopic residual tumor size, pelvic and paraaortic lymph node metastasis, and cervical involvement were found to be poor prognostic factors. In multivariate analyses, optimal cytoreduction was found to be associated with prolonged survival.[22] Lambrou et al. performed primary cytoreduction in 85 patients with advanced stage (66 stage 3, 19 stage 4) endometrial adenocarcinoma and found that survival was shorter and morbidity increased in patients who underwent suboptimal cytoreduction. They found that survival was 17.8 months in patients with optimal cytoreduction and 6.7 months in patients with suboptimal cytoreduction. [23]

A meta-analysis of 14 studies by Barlin et al. showed that optimal cytoreduction had a significant contribution to median survival. According to this study, each 10% increase in the proportion of patients undergoing optimal cytoreduction leads to a 9.3-month survival increase. According to this study, the aim of advanced-stage endometrial carcinoma should be the resection of all visible tumorous tissues.[16]

In our study, median survival could not be calculated because the number of patients who died was not sufficient; instead, mean survival was used. Optimal cytoreduction was accepted as residual disease of 1 cm or less. Accordingly, mean survival was 119 ± 10 months in patients with optimal cytoreduction and 22 ± 6 months in patients with suboptimal cytoreduction was found. These data show that patients with optimal cytoreduction have better survival than patients with suboptimal cytoreduction, which is consistent with the literature. This significance was maintained in multivariate analyses.

CONCLUSION

In our study, optimal cytoreduction was defined as residual disease with a tumor size of 1 cm or less. Accordingly, there is a significant correlation between optimal cytoreduction and survival. This information was found to be consistent with the literature. Further studies with large case series may provide a clearer idea about this issue.

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DERLEME REVIEW

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Over kanseri, sirkadiyen ritim ve kronokemoterapi

Ovarian cancer, circadian rhythm and chronochemotherapy

Yağmur SOYKAN[1,2], Atiye Seda YAR SAGLAM[2]

[1]Gazi Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Bilim Dalı Ankara, Türkiye
[2]Gazi Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji ve Genetik Anabilim Dalı, Ankara, Türkiye

ÖZ

Over kanseri kadınlar arasında yaygın görülen ölümcül bir hastalıktır ve jinekolojik kansere bağlı ölümlerin önde gelen nedenlerinden biridir. Tedavisi tipik olarak sitoredüktif cerrahi ve adjuvan kemoterapinin bir kombinasyonunu içerir. Ancak kemoterapinin yan etkileri tedavi sürecinde önemli zorluklar yaratabilir. Son yıllarda sirkadiyen ritmin kanser gelişimindeki rolü giderek daha fazla dikkat çekmektedir. Sirkadiyen ritim, vücudun fizyolojik süreçlerini 24 saatlik döngülerle düzenleyen bir iç biyolojik saat olarak işlev görür ve bu ritimdeki bozulmalar kanser riskini artırabilir. Kronoterapi, ilaçların vücudun biyolojik saatiyle senkronize bir şekilde, özellikle de sirkadiyen ritmi takip ederek uygulanmasını amaçlayan bir yaklaşımdır. Kronokemoterapi, hastanın sirkadiyen ritmine göre optimize edilmiş kemoterapötik ajanların zamanlamasını ifade eder. Bu yöntemin temel amacı, ilaçların kanser hücreleri üzerindeki etkisini artırırken sağlıklı hücreler üzerindeki toksik etkilerini azaltmaktır. Kronokemoterapinin over kanseri tedavisindeki potansiyeli umut verici olsa da, bu alandaki klinik kanıtlar sınırlı kalmaktadır. Mevcut çalışmaların çoğu küçük ölçeklidir ve genellikle çelişkili sonuçlar vermektedir. Bu nedenle, kronokemoterapinin over kanseri tedavisindeki rolünü tam olarak anlamak için daha büyük, iyi tasarlanmış klinik çalışmalar gereklidir. Gelecekteki araştırmalar, genetik ve çevresel faktörleri hesaba katan, tedavi zamanlamasını optimize eden ve over kanserinde biyolojik saat genlerinin rolünü daha fazla araştıran kişiselleştirilmiş tedavi yaklaşımları geliştirmek için çok önemlidir. Ayrıca, sirkadiyen ritimlerdeki bireysel farklılıklar ve hastaların tedavi protokollerine uyumu gibi kronokemoterapinin klinik uygulamaya entegre edilmesindeki zorluklar da ele alınmalıdır.

Anahtar Kelimeler: Over kanseri, sirkadiyen ritim, kronokemoterapi

ABSTRACT

Ovarian cancer is a prevalent and fatal disease among women, representing one of the leading causes of gynecological cancer-related deaths. Treatment typically involves a combination of cytoreductive surgery and adjuvant chemotherapy. However, chemotherapy's side effects can present significant challenges during the treatment process. In recent years, the role of circadian rhythm in cancer development has gained increasing attention. Circadian rhythm functions as an internal biological clock, regulating the body's physiological processes on 24-hour cycles, and disruptions in this rhythm may increase cancer risk. Chronotherapy is an approach that aims to administer drugs in synchronization with the body's biological clock, specifically following the circadian rhythm. Chronochemotherapy refers to the timing of chemotherapeutic agents optimized for the patient's circadian rhythm. The primary goal of this method is to reduce the toxic effects of drugs on healthy cells while enhancing their impact on cancer cells. While the potential of chronochemotherapy in treating ovarian cancer is promising, clinical evidence in this area remains limited. Most available studies are small-scale and often yield contradictory results. Thus, larger, well-designed clinical trials are essential to fully understand the role of chronochemotherapy in ovarian cancer treatment. Future research is crucial for developing personalized treatment approaches that account for genetic and environmental factors, optimize treatment timing, and further investigate the role of biological clock genes in ovarian cancer. Additionally, challenges in integrating chronochemotherapy into clinical practice, such as individual differences in circadian rhythms and patient adherence to treatment protocols, must be addressed.

Keywords: Ovarian cancer, circadian rhythm, chronochemotherapy

GİRİŞ

Over kanseri, kadın üreme sisteminde bulunan yumurta hücrelerinin kontrolsüz çoğalmasından kaynaklanan ölümcül bir hastalıktır. Jinekolojik kanserlerden ölümlerin en sık nedeni over kanseridir (1). Kadınlarda görülen kanserlerin %4'ünü ve kadın genital sistem kanserlerinin %25'ini oluşturmaktadır. 5 yıllık sağ kalım oranının ise %37 olduğu bildirilmiştir (2). Geç dönemde belirti verdiğinden %70-80'i ileri evrede yakalanmaktadır. Tedavisi sitoredüktif cerrahi ve adjuvan kemoterapidir. Erken evredeki bazı olgular hariç (evre 1a, grad1, grad2) tüm hastalara kemoterapi uygulanır. Over kanserinin prognozu, hastalığın evresine, histolojik tipine, tümör derecesine ve hastanın genel sağlık durumuna bağlıdır. Erken evre hastalıklarda vakaların yaklaşık %25'inde, ileri evrelerde ise %80'den fazlasında nüks görülmektedir (3).

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Sorumlu Yazar/Corresponding Author: Yağmur SOYKAN, Gazi Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Bilim Dalı Ankara, Türkiye
E-mail: dr.soykan@hotmail.com

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Over kanseri risk faktörleri arasında aile öyküsü ve kalıtsal genetik yatkınlık [BReast CAncer 1 (BRCA1) ve BRCA 2 gen mutasyonu, Lynch Sendromu, ailede meme kanseri öyküsünün olması], ileri yaş, nulliparite, geç menopoz, postmenopozal hormon replasman tedavisi, diyet, sigara kullanımı yer alır (4). Genetik yatkınlığın yanı sıra, çevresel ve yaşam tarzı faktörlerinin de over kanseri gelişiminde önemli rol oynadığı düşünülmektedir (4).

Over kanseri; epitelyal over tümörleri, germ hücreli over tümörleri, seks kord stromal tümörler ve metastatik tümörler olmak üzere farklı gruplara ayrılmaktadır. Over kanserinin etkin bir tarama yöntemi yoktur ve asemptomatik kadınların pelvik muayene, pelvik ultrasonografi veya tümör belirteçleri ile taranması önerilmemektedir. BRCA gen mutasyonu olan kadınlarda bile transvajinal ultrasonografi ve Kanser Antijen 125 (CA-125) ile taramanın yapılmasının çok sınırlı bir faydası görülmüştür ve umut vaad etmemektedir (5).

Klinik bulguları arasında, bulantı, non spesifik pelvik, abdominal ve menstrual semptomlar mevcuttur. Erken evre hastalığı olanlarda en sık pelvik ağrı, ileri evre hastalığı olanlarda ise en sık abdominal şişkinlik izlenmekte olup bunlar non spesifik semptomlar olup tanıda gecikmeye neden olmaktadır. En önemli bulgu pelvik kitlenin saptanmasıdır. Solid, fikse, irregüler kitle over kanseri açısından şüphe uyandırır. Müsinöz over tümörlerinde CA19-9 ve Karsinoembriyonik Antijen (CEA) daha iyi bir serum belirteci iken, non müsinöz malign over tümörlerinde ise %90 CA-125 düzeyi yükselebilmektedir. Kullanılabilecek bir diğer tümör belirteci İnsan Epididimal Protein-4 (HE-4) olup, CA-125 ile birlikte Risk of Malignancy Algoritm (ROMA) indeksinin belirlenmesinde FDA onayı almıştır. Preoperatif hastaların yönetimi için OVA1 skoru kullanılabilir. Ancak bu test tarama testi değildir (6).

Over kanseri tanısı için rezeke edilen overin histopatolojik incelenmesi gereklidir. Tedavi seçenekleri arasında cerrahi müdahale, kemoterapi, hedefe yönelik tedavi, hormonoterapi ve radyoterapi bulunur. Over kanseri cerrahi olarak evrelenir. Tedavi şekli, kanserin evresine, histolojik tipine, derecesine, hastanın genel sağlık durumuna göre belirlenir. İleri evre over kanseri tespit edilen ve medikal açıdan stabil hastalarda primer tümör ve ilişkili metastatik hastalığın eksize edildiği sitoredüktif (debulking) cerrahi uygulanır. Sitoredüktif cerrahi total abdominal histerektomi ve bilateral salpingoooferektomi, bulky lenf nodlarının diseksiyonu, total omentektomi ve peritoneal yüzeyler ve tüm metastatik lezyonların rezeksiyonunu kapsamaktadır. Genellikle platin bazlı ajanlar (örn. Karboplatin + Paklitaksel) standart tedavidir (7). Neoadjuvan (cerrahiden önce) veya adjuvan (cerrahiden sonra) olarak uygulanabilir.

Kemoterapi

Over kanseri tedavisi, cerrahi müdahale, kemoterapi ve hedefe yönelik tedavilerin kombinasyonunu içerir. Özellikle epiteliyal over kanserinde (EOC) kemoterapi, standart bir tedavi yöntemidir. Kemoterapi, over kanseri hücrelerindeki temel hücresel süreçleri etkili bir şekilde hedef alsa da, ilaç direnci ve toksisite gibi zorluklar önemli endişeler yaratmaya devam etmektedir. Kemoterapi alanında da yeni ajanlar ve kombinasyonlar geliştirilerek tedavi seçenekleri genişletilmektedir ancak geleneksel kemoterapi uygulamalarında, ilaçların vücut üzerindeki etkileri zamandan bağımsız olarak ele alınmaktadır. Kemoterapiye bağlı olarak hastalarda bir çok yan etki görülmektedir. Kemoterapi, kanser hücrelerinin DNA'sına hasar vererek kanser hücrelerini yok etmeye çalışırken sağlıklı hücrelere de zarar verir.

Kronoterapi, ilaçların biyolojik saatimiz olan sirkadiyen ritimle uyumlu bir şekilde uygulanmasını amaçlar. Sirkadiyen ritim, vücudumuzdaki temel fizyolojik süreçleri düzenler ve hücresel aktiviteleri etkiler ve bu ritim, kemoterapi ilaçlarının metabolizmasını, dolayısıyla da etkinliğini ve toksisitesini etkileyebilir. Kronokemoterapi ise kemoterapi ilaçlarının, hastanın sirkadiyen ritmine göre optimize edilmiş zamanlarda uygulanması anlamına gelir. Amaç, ilaçların etkinliğini artırırken, yan etkilerini minimuma indirmektir. Bu yaklaşım, over kanseri tedavisinde umut verici bir alan olarak öne çıkmakta ve tedavi sonuçlarını iyileştirme potansiyeline sahip görünmektedir. Sirkadiyen ritmin bu etkisini göz önünde bulundurarak geliştirilen kronokemoterapi, tedavi sonuçlarını iyileştirme potansiyeline sahiptir.

Sirkadiyen Ritim

Overler, insan üreme sağlığıyla yakından ilişkili olan belirli döngüsel aktivitelere sahiptir, ancak over kanserinin biyoritmi, oluşumu ve düzenlenme mekanizması net değildir. Overlerin üreme döngüsünün (hipotalamus-hipofiz-over (HPO)) sirkadiyen ritimlerden etkilendiği ve ritimlerinin nörolojik ve endokrin dokular tarafından koordine edildiği ve senkronize edildiği bulunmuştur (8).

Sirkadiyen ritim, vücutta 24 saatlik döngüde ritmik olarak meydana gelen fizyolojik, kimyasal ve moleküler olayları içeren günlük biyolojik ritmi tanımlar. Bu içsel biyolojik saat, memelilerde hipotalamusta yer alan suprakiyazmatik nükleus (SKN) adı verilen özel bir nöron topluluğu tarafından yönetilir. Sirkadiyen genler, hücre proliferasyonu, apoptoz, hücre döngüsü kontrolü ve DNA hasar onarımı gibi süreçlerin düzenlenmesinde rol oynayarak, hücresel ve moleküler düzeyde tümör baskılayıcı fonksiyonlar sergilerler (9).

Uyku, yeme alışkanlıkları, kalp hızı, vücut ısısı ve hormon üretimi gibi zamana bağlı biyolojik fonksiyonları kontrol eden çok sayıda "saat-ilişkili" gen bulunmaktadır. Sirkadiyen ritim ve bu ritme

ait genler, karsinom hücrelerinin gelişiminde ve yayılmasında rol oynayabilir. Memeli genomunun yaklaşık %10'u saat kontrollü genlerden oluşmaktadır (10). Bugüne kadar, Circadian locomotor output cycles kaput (Clock), BMAL1 (ARNTL veya MOP3 olarak da bilinir), Period1, Period2, Period3 (Per1, Per2, Per3), Cryptochrome1, Cryptochrome2 (Cry1, Cry2), Timeless (TIM), CK1ε, REV-ERB (NRD1 olarak da bilinir), DEC1, DEC2, ROR, ve NPAS2 olmak üzere 14 genin sirkadiyen ritimde rol oynadığı belirlenmiştir (11). Bu moleküller, hücresel saat mekanizmasında önemli roller üstlenen otoregülatörlerdir ve sirkadiyen ritmin düzenlenmesi için transkripsiyon ve translasyon süreçleri aracılığıyla etkileşime girerler. BMAL1 ve Clock, sitoplazmada heterodimerler oluşturarak nükleusa transloke olurlar ve Per ve Cry genlerinin transkripsiyonunu aktive ederler. Per ve Cry proteinleri kompleks halinde hücre sitoplazmasında gece boyunca birikirken, gündüzleri degradasyona uğrarlar. Bu sayede, 24 saatlik gece/gündüz döngüsünde sirkadiyen ritim ile uyumlu olarak ritmik dalgalanmalar gösterirler. Gece boyunca sitoplazmada biriken Per ve Cry proteinleri, kazein kinaz 1 ile kompleks oluşturarak nükleusa taşınır ve kendi transkripsiyonel aktivitelerini de inhibe ederler. Dolayısıyla, geri bildirimin hızı ve ritmisite, bu döngüye katılan proteinlerin fosforilasyon durumu, stabilitesi ve nükleer lokalizasyonu ile kontrol edilir. Elde edilen ritmik bilgi, promotor bölgelerinde E-box veya RRE sekansları içeren saat kontrollü genlerin ritmik transkripsiyonu aracılığıyla genomun geri kalanına iletilir. SKN'dan bağımsız olarak, periferik organlarda da sirkadiyen saat genleri ritmik bir şekilde eksprese edilir. Farklı kanser türlerinde farklı sirkadiyen genlerin ekspresyonu değişiklik göstermektedir. Örneğin, over kanserinde BMAL1 ekspresyonunun (12), endometrium kanserinde ise CLOCK, NPAS2, CSNK1D ve PER3 ekspresyonunun farklı biyolojik rolleri olduğu gösterilmiştir (13).

Yapılan bir çalışmada, sekiz çekirdek saat geninin ekspresyon seviyeleri - PER1, PER2, PER3, CRY1, CRY2, BMAL1, CLOCK ve CKlepsilon - gerçek zamanlı kantatif ters transkripsiyon-polimeraz zincir reaksiyonu (PCR) kullanılarak 83 over kanseri örneğinde ve 11 normal over dokusunda ölçülmüştür. PER1, PER2, CRY2, CLOCK ve CKlepsilon'un ekspresyon seviyelerinin over kanseri dokularında normal over dokularına kıyasla önemli ölçüde daha düşük olduğu bulunmuştur. Buna karşılık, CRY1, kanser dokularında eksprese edilen saat genleri arasında en yüksek ifadeyi sergilemiştir, onu PER3 ve BMAL1 izlemiştir. In situ hibridizasyon analizi, CRY1'in müsinöz ve grade 3 tümörlerde önemli ölçüde azaldığını, BMAL1 ekspresyonunun ise müsinöz adenokarsinomlarda diğer tiplere kıyasla daha düşük olduğunu göstermiştir. Çok değişkenli analiz, klinik evre ve histolojik alt tip ile birlikte CRY1 ve BMAL1'in düşük ekspresyonunun bağımsız prognostik faktörler olarak hizmet ettiğini ortaya koymuştur. Bu bulgular, biyolojik saat genlerinin over kanserindeki rolüne ve potansiyel prognostik belirteç olarak kullanımına işaret etmektedir (12).

Yeh ve arkadaşlarının yaptığı çalışmada, over kanseri hücrelerinde ARNTL geninin epigenetik olarak susturulduğu gösterilmektedir. ARNTL geninin promotör bölgesi, DNA metilasyonu ve baskılayıcı histon modifikasyonları ile zenginleştirilmiştir. ARNTL ifadesinin geri kazandırılması, hücre büyümesini inhibe etmiş, cisplatin kemoterapisine duyarlılığı artırmış ve c-MYC geninin ritmik aktivitesini yeniden sağlamıştır. Bu bulgular, ARNTL geninin over kanserinde bir tümör baskılayıcı görevi görebileceğini ve epigenetik susturulmasının kanser gelişiminde rol oynayabileceğini düşündürmektedir (13).

Bir başka çalışmada ise, over kanserinde biyolojik saatle ilişkili 15 önemli gen belirlemiştir. RORC'nin mRNA seviyesi up regüle edilirken, over kanseri dokularında normal dokulara göre ARNTL, CRY2, NR1D1, PER1, PER3 ve RORA'nın ekspresyonlarının azaldığı gözlenmiştir. Sirkadiyen saat genlerinin over kanserinde gen düzeyinde geniş çapta değiştirildiğini göstermektedir. Sirkadiyen saat ile over kanserindeki ilerleme ve prognoz arasında olası bir bağlantı olduğunu göstermektedir. Bu genler, hastaların hayatta kalma oranları ve tümörün bağışıklık mikroçevresi ile ilişkilidir. Yüksek biyolojik saat indeksi (CCI) kötü prognozu gösterirken, CCI aynı zamanda bağışıklık belirteçleri ve steroid hormonlarla ilişkili genlerle de bağlantılıdır. Bu bulgular, over kanserinin moleküler mekanizmalarını daha iyi anlamak için yeni yollar sunmaktadır (14).

Fahrenkrug ve arkadaşlarının yapmış olduğu çalışma ise, sıçan overlerinde Per1 ve Per2 olmak üzere iki temel biyolojik saat geninin 24 saatlik bir ritimle ifade edildiğini göstermektedir. Bu ritmik ifade, östrus döngüsünün farklı evrelerinde ve sürekli karanlık koşullarında bile korunmaktadır. Per1 ve Per2 mRNA'ları ve proteinleri, steroid hormon üreten hücrelerde lokalizedir. Bu bulgular, overlerde bir biyolojik saatin varlığını ve bu saatin hem yerel olarak hem de hipotalamus-hipofiz-yumurtalık ekseninde rol oynayabileceğini düşündürmektedir (15).

Sirkadiyen ritim, vücudun biyolojik saatinin düzenlediği ve hücrelerin, organların ve sistemlerin zamanlamasına dayanan karmaşık bir süreçtir. Kanser gelişimi, ilerlemesi ve tedaviye yanıtı üzerinde bu ritmin bozulmasının belirgin etkileri olduğu gösterilmiştir. Elde edilen bulgular, sirkadiyen ritmin hem kanser gelişiminde hem de tedavi sürecinde önemli bir faktör olduğunu ve bu alana yönelik müdahalelerin hastalığın seyrini olumlu yönde etkileyebileceğini destekler niteliktedir.

Sirkadiyen ritmin kanser gelişimindeki rolü

Sirkadiyen ritimde meydana gelen bozukluklar, kanser riskini önemli ölçüde artırabilen ve kanser gelişimini hızlandırabilen karmaşık bir süreci tetikleyebilir. Bu bozukluklar, hücre döngüsü kontrolü, DNA onarımı, metabolizma, bağışıklık sistemi fonksiyonları ve hormon

salınımı gibi temel hücresel süreçleri olumsuz yönde etkileyebilir. Dolayısıyla, sirkadiyen ritmin korunması ve ritim bozukluklarının düzeltilmesi, kanseri önleme ve tedavi stratejilerinde kritik rol oynamaktadır. Bu nedenle, sirkadiyen ritmin kanser oluşumu üzerindeki etkileri, çeşitli mekanizmalar aracılığıyla kendini gösterir ve bu mekanizmaların anlaşılması, etkili önleme ve tedavi stratejileri geliştirmek için gereklidir.

Hücre Döngüsü ve Kontrolsüz Proliferasyon: Sirkadiyen ritim, hücre döngüsünün düzenlenmesinde ve hücresel proliferasyonun kontrol altında tutulmasında hayati bir öneme sahiptir. Bu ritimdeki aksamalar, hücrelerin kontrolsüz bir şekilde büyümesine zemin hazırlayarak kanser gelişimine katkıda bulunabilir (16).

DNA Hasarı ve Onarım Mekanizmaları: Sirkadiyen saat genleri, DNA hasarının onarılması ve genetik bütünlüğün korunması süreçlerinde aktif rol oynar. Bu ritimdeki bozulmalar, DNA onarım mekanizmalarının etkinliğini azaltabilir ve kanser riskini artırabilir (17).

Hormon Salınımının Düzenlenmesi: Melatonin gibi hormonlar, sirkadiyen ritimle uyumlu bir şekilde salgılanır ve anti-kanser özelliklere sahip olduğu düşünülmektedir. Melatonin üretimindeki aksamalar, özellikle gece vardiyasında çalışan bireylerde kanser riskinin artmasıyla ilişkilendirilmiştir (18).

Bağışıklık Sistemi Fonksiyonları: Sirkadiyen ritim, bağışıklık sisteminin işleyişini doğrudan etkileyerek bağışıklık hücrelerinin etkinliğini ve kanser hücrelerine karşı verdikleri yanıtı düzenler (19).

Kronobiyolojik Yaklaşımlar ve Tedavi Stratejileri: Kanser tedavilerinin sirkadiyen saat dikkate alınarak zamanlanması (kronoterapi), tedavi etkinliğini artırabilir ve yan etkileri en aza indirebilir. Belirli kanser ilaçlarının günün belirli saatlerinde uygulandığında daha etkili olduğu gösterilmiştir (20).

Özetle, sirkadiyen ritmin kanser üzerindeki çok yönlü etkileri, bu biyolojik saatin korunmasının ve ritim bozukluklarının düzeltilmesinin kanserle mücadelede önemli bir strateji olduğunu vurgulamaktadır.

Sirkadiyen ritim ve hücre döngüsü

Sirkadiyen ritim, hücre döngüsünün çeşitli aşamalarını düzenleyen genlerin ekspresyonunu kontrol eder. CDK1/siklin B1 kompleksi, mitozu başlatmaktan sorumlu olup, ekspresyonu sirkadiyen olarak Wee1 tarafından düzenlenir. Wee1'in ekspresyonu, CLOCK/BMAL1 aktivasyonu ve PER/CRY inhibisyonu ile gün boyunca değişir. PER1 proteini, Wee1'i engelleyerek ve Chk1 ile etkileşime girerek p16-INK4A genini kontrol ederek hücre döngüsü kontrolüne katkıda bulunur. Buna karşılık, c-Myc'in ekspresyonu CLOCK/BMAL1 tarafından inhibe edilir ve PER1 tarafından stabilize edilmesi, p21'in ekspresyonunu engelleyerek hücre döngüsünün devam etmesine olanak tanır (21).

Klevecz ve arkadaşları, over kanseri olan 30'dan fazla hastadan aldıkları karın içi sıvısında tümör ve normal mezotel hücrelerindeki replikasyon aşamalarını incelemişlerdir. Hücre döngüsünün farklı evrelerindeki hücrelerin oranlarını (G2 ve S fazları) belirlemek için 72 saat boyunca her 1-3 saatte bir alınan örnekler analiz edilmiştir. Over kanseri hücrelerinin çoğalmasının, normal hücrelerden farklı bir döngüsel ritim izlediğini, tümör hücrelerinde S fazındaki hücrelerin oranının, normal dokuların günlük ritmine göre farklı zamanlarda zirve yaptığını saptamışlardır. Bu durum, kemoterapinin tümör hücrelerinin en savunmasız olduğu ve normal dokuların en az etkilendiği zamanlara denk getirilmesi için bir fırsat sunmaktadır (22).

Tedavi sürecinde sirkadiyen ritmin rolü:

Tedavi sürecinde sirkadiyen ritmin dikkate alınması, ilaçların etkinliğini ve güvenliğini optimize etmeye, bağışıklık yanıtını güçlendirmeye, radyoterapi ve hormonal tedavilerin başarısını artırmaya ve hastaların uyku kalitesini ve yaşam kalitesini iyileştirmeye yardımcı olabilir. Bu nedenle, kanser tedavisinde kronoterapi ve sirkadiyen ritim uyumlu yaklaşımlar giderek daha fazla araştırılmakta ve uygulanmaktadır. Yapılan bir çalışmada Cry1/2 ve p53 mutasyonlarına sahip tümörlerin, sadece p53 mutasyonu taşıyan tümörlere kıyasla kemoterapötik ilaçlara daha duyarlı olduğu saptanmıştır. Bu moleküllerin tedavi üzerindeki etkileri, özellikle Cry gen baskılayıcılarının kullanımı yoluyla kemoterapinin etkinliğini artırma potansiyeli açısından önem arz etmektedir (23).

Müdahalelerin olumlu etkisi:

Sirkadiyen ritmin düzenlenmesine yönelik müdahaleler (uyku hijyeninin optimizasyonu, düzenli fiziksel aktivite, melatonin gibi sirkadiyen ritim düzenleyici ajanlar, ışık terapisi) kanser tedavisinin başarısını artırma potansiyeline sahiptir. Bu tür yaklaşımlar, hastaların psikolojik sağlığını iyileştirebilir, fiziksel iyileşme süreçlerini hızlandırabilir ve tedaviye yanıtlarını optimize edebilir. Ayrıca, sirkadiyen ritmin senkronizasyonu, kemoterapi gibi tedavi modalitelerinin yan etkilerini azaltarak hastaların yaşam kalitesini artırabilir.

Kronokemoterapi

Sirkadiyen ritim, temel hücresel süreçleri (hücre bölünmesi, DNA tamiri, apoptoz) düzenlemenin yanı sıra, kanser gelişiminde rol oynayan metabolik yolaklar ve işlevler üzerinde de önemli bir etkiye sahiptir (24). Bu nedenle, sirkadiyen ritmin kanser tedavisindeki potansiyeli, özellikle kemoterapinin etkinliğini artırma açısından büyük bir önem taşımaktadır. Kemoterapi ilaçları kanser hücrelerinde DNA hasarı oluşturarak etki gösterirken, sağlıklı hücrelere de zarar

verebilir (25). İşte bu noktada kronoterapi devreye girmektedir. Kronoterapi, ilaçlardan en üst düzeyde fayda sağlamak ve yan etkilerini en aza indirmek amacıyla tedavinin günün belirli saatlerinde uygulanmasıdır. Bu yaklaşım, ilk olarak 1970'lerin başında kanser araştırmalarında keşfedilmiş olup, klinik araştırmalar antikanser ilaçlarının farklı zaman noktalarında farklı zirvelere ulaştığını ve ilaç toksisitesinin değiştiğini göstermiştir (26). Kemoterapötik ajanların çoğu, tümör hücrelerinde DNA hasarını indükleyerek etki gösterdiğinden, sirkadiyen ritim ve DNA hasarı arasındaki ilişkinin aydınlatılması, kronokemoterapinin yaygınlaşmasını sağlayabilir. Buna göre, hücrelerimizde DNA onarımının zirvede olduğu zaman aralığında hastalara kemoterapi verilmesinin daha yararlı olabileceği düşünülmektedir. Bu doğrultuda, hücrelerde DNA onarımının en yoğun olduğu zaman diliminde kemoterapi uygulanmasının, toksik yan etkileri azaltırken tedavi etkinliğini artırabileceği düşünülmektedir. Yapılan kronokemoterapötik bir çalışmada, farelere 24 saatlik süre boyunca toplam 240 mg/kg arabinosil sitozin (ara-C) verilmiştir. Endojen sirkadiyen salınımlara dayalı tedavi grubuna, her üç saatte bir standart 30 mg/kg yerine, farelerin en toleranslı olduğu döngünün başlarında en yüksek dozlar verilmiştir (ilk dört doz, 24 saatlik döngüdeki son dört dozdan iki kat daha yüksekti). Kronoterapötik tedavi grubundaki fareler önemli ölçüde daha uzun süre hayatta kalmış, aynı zamanda daha yüksek kemoterapi dozlarına toleranslı oldukları görülmüştür (27). Kronokemoterapi uygulamaları, tedavi sürecini daha verimli hale getirerek hasta yanıtlarını iyileştirme potansiyeline sahip olabilir.

Over kanserinde adjuvan kemoterapide yaygın olarak karboplatin ve paklitaksel kombinasyonu kullanılmaktadır (28). Karboplatin, alkilleyici ajanlar sınıfına ait bir platin bazlı kemoterapi ilacıdır (29). DNA baz çiftlerinin alkil gruplarına bağlanarak DNA zincirlerinde çapraz bağlar oluşturarak veya hatalı nükleotid eklenmesi yoluyla mutasyonlara neden olarak DNA replikasyonunu inhibe eder. Karboplatinin gastrointestinal yan etkileri (bulantı, kusma) sık görülmekle birlikte, nefrotoksisite, nörotoksisite ve ototoksisite gibi toksik etkiler daha az sıklıkta gözlenir. Paklitaksel ise, mikrotübül stabilizasyonunu sağlayarak kanser hücresinin proliferasyonunu engelleyen bir taksan türevidir. Major yan etkileri arasında kemik iliği supresyonu, gastrointestinal semptomlar ve alopesi bulunmaktadır. Bu kemoterapotik ilaçların yan etkileri, tedavi sürecinde önemli bir engel teşkil ederek hasta uyumunu zorlaştırabilir. Bu nedenle, bu tedavilerin etkinliğini artırırken yan etkilerini en aza indirme stratejileri geliştirmek büyük önem taşır. Kronokemoterapi, kanser ilaçlarının optimal biyolojik saatte uygulanarak yan etkilerin minimize edilmesini hedeflemektedir. Over kanserinde sirkadiyen ritmin yeniden düzenlenmesi ve kronoterapi gibi yaklaşımların geliştirilmesi, tedavi etkinliğini artırabilir ve hasta sonuçlarını iyileştirebilir. Karboplatin gibi kemoterapi ilaçlarının en etkili olduğu zaman dilimlerinde uygulanması, tümör hücrelerinin yok edilmesinde daha yüksek verimlilik sağlayabilir. Sirkadiyen ritme uygun Karboplatin uygulamaları, hücrelerin biyolojik saatiyle uyumlu zamanlarda daha etkili DNA hasarını ve apoptozu indükleyebilir, aynı zamanda sağlıklı hücrelerin bu süreçten daha az zarar görmesini sağlayabilir.

Mayıs 2018'de Aziz Sancar ve ekibi tarafından yayınlanan bir çalışmaya göre, sağlıklı hücrelerde DNA tamirinin en yoğun olduğu zamanda sisplatin uygulanması, tedavi sonuçlarını iyileştirebilir; yani sirkadiyen ritme göre tedavinin düzenlenmesi sonucunda kemoterapinin yan etkilerini azaltabileceği gözlenmiştir (30). Sisplatin, nefrotoksisite, hepatotoksisite ve nörotoksisite gibi ciddi yan etkilere sahiptir. Söz konusu çalışmada bu sınırlamaların üstesinden gelmek amacıyla kemoterapi günün belirli saatlerinde uygulanmış, ancak sınırlı başarı elde edilmiştir (31). Kronokemoterapi uygulamaları, daha fazla araştırma ve uzun dönemli klinik çalışmalarla desteklendiğinde, özellikle belirli kanser türlerinde ve hasta gruplarında daha fazla fayda sağlayabilir.

İlginç bir şekilde, 2020 yılında yayınlanan ve 8.477.849 katılımcının yer aldığı 57 gözlemsel çalışmanın sistematik incelemesini rapor eden bir makalede (DSÖ sonucunun temelini oluşturan çalışmalar da dahil olmak üzere) gece vardiyalı çalışmaya maruz kalma ile meme, prostat, over, pankreas, kolorektal, Hodgkin dışı lenfoma ve mide kanseri riski arasında genel bir ilişki bulunamamıştır (32). Yapılan bir başka çalışmada ise metastatik kolorektal kanser tedavisinde kronoterapinin etkinliğine dair olumlu sonuçlar rapor edilmiştir (33, 34). Cinsiyet temelli bir analizde kronoterapi, metastatik kolorektal kanserli erkek hastalarda geleneksel tedaviye göre daha uzun sağkalım sağlarken, kadınlarda anlamlı bir fark gözlenmemiştir. Bu nedenle, erkek hastalar için kronoterapi metastatik kolorektal kanser tedavisinde daha güvenli ve etkili bir alternatif olabilir (35). Kronoterapinin kanser tedavisindeki sonuçları umut verici ve uygulanabilir olsa da, yaş, cinsiyet veya kronotip gibi faktörler göz önünde bulundurulmalıdır.

Over kanserinin kronokemoterapisine ilişkin az sayıda denekle yapılan bir klinik çalışmada ise, doksorubisin ve sisplatin kronoterapisi ile 5 yıllık hastalıksız sağ kalımda, geleneksel ilaç uygulaması alan deneklere kıyasla 4 kat artış bildirilmiştir (36, 37). Takip eden büyük ve çok merkezli bir çalışma bu ön raporu doğrulamamıştır ve şu anda kronoterapi Amerikan Jinekolojik Onkoloji Grubu tarafından uygulanmamaktadır (38).

18 çalışma ve 2547 hasta içeren bir sistematik incelemede, kanser tedavisinde uygulanan kronomodüle edilmiş kemoterapinin, geleneksel kemoterapiye kıyasla toksisiteyi azaltma eğiliminde olduğu ve etkinliği koruduğunu göstermektedir (39). Kireeva ve arkadaşlarının yaptıkları çalışmada ise, sıçanlarda over kanseri

modelinde tümör büyümesinin biyolojik ritimleri bozduğunu ve bu durumun tedavi yanıtını etkileyebileceğini gösterilmektedir. Sabah saatlerinde 8:00 (ZT0) uygulanan hipertermik intraperitoneal kemoterapi (HIPEC) tedavisinin, hem gece 20:00 (ZT12) uygulanan HIPEC'e hem de intravenöz uygulamaya kıyasla daha iyi etkinlik ve toksisite profiline sahip olduğu bulunmuştur (40).

Erken dönem insan çalışmaları, ileri evre over kanseri hastalarında doksorubisinin sabah (6:00) ve sisplatin'in akşam (16:00-20:00) uygulanmasının, akşam doksorubisin ve sabah sisplatin uygulanmasına kıyasla daha az komplikasyon ve böbrek toksisitesi ile birlikte doz azaltmaları ve tedavi gecikmeleriyle sonuçlandığını göstermiştir. Bu programla tedavi edilen hastaların 5 yıllık hayatta kalma olasılığı %44 olarak belirlenmiştir. Ayrıca, benzer şekilde sabah pirarubisin ve akşam sisplatin ile tedavi edilen yumurtalık kanseri hastalarında da olumlu sonuçlar elde edilmiştir (41).

Mevcut kanıtlar, sirkadiyen ritm değişikliklerin etkisinin tümör tipine göre değiştiğini ve her kanser kategorisinin saat genlerini ve onkogenleri içeren benzersiz moleküler etkileşimler sunduğunu gösterdiğini göstermektedir. Bu karmaşıklık, sirkadiyen ritm genlerinin rolünü doğrulamak, ilaç geliştirme için en uygun hedefleri belirlemek ve hastalığa özgü bir yaklaşım gerektirir. Literatürde, biyolojik saatin kanser riski, gelişimi ve ilerlemesiyle ilişkili olduğunu belirtilmektedir (42).

Şimdiye kadarki klinik çalışmalar, optimal tedavi zamanlamasının ilaç toksisitesini azaltabileceğini, etkinliği artırabileceğini ve daha doz yoğun ancak başarılı bir tedaviye izin verebileceğini doğrulamıştır. Bu nedenle, kemoterapi ile kronoterapi kombinasyonu umut verici bir terapötik araç gibi görünmektedir. Kronokemoterapi, over kanseri tedavisinde gelecek vaat eden bir yaklaşım olmasına rağmen, güncel klinik uygulamalarda deneysel bir tedavi modalitesi olarak değerlendirilmelidir ve klinik uygulamaya tam olarak entegre edilebilmesi için daha fazla randomize kontrollü çalışmaya ihtiyaç vardır. Tedavi kararları, kronokemoterapinin etkinliği ve güvenirliğine dair henüz yeterli kanıt bulunmadığı, geniş kapsamlı randomize kontrollü çalışmaların (RKÇ) gerekliliği ve potansiyel yarar-zarar dengesinin her hasta özelinde titizlikle değerlendirilmesi gerektiği dikkate alınarak verilmelidir. Devam eden araştırmalar, kronokemoterapi ile ilgili bilgi birikimimizi artırarak, bu yaklaşımın gelecekte daha etkili ve güvenli bir tedavi seçeneği haline gelmesine katkıda bulunabilir. Bu alanda yürütülecek ileri çalışmalar, tedavi zamanlaması stratejilerinin optimizasyonuna ve kişiselleştirilmesine olanak sağlayacaktır. Gelecekte, kişiselleştirilmiş tedavi yaklaşımlarıyla kemoterapinin zamanlaması kişiye özel olarak belirlenebilir, böylece tedavi etkinliği artırılıp toksisite en aza indirilebilir.

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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

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Bordotella pertussis during pregnancy: do we need to increase vaccination?

Gebelikte bordotella pertussis: Aşılamayı artırmamız gerekir mi?

Nizamettin BOZBAY[1], Gokcen ORGUL[2]

[1,2]Department of Perinatology, Selcuk University Faculty of Medicine, Konya, Türkiye

Dear Editor

While pertussis caused by Bordetella pertussis often proceeds asymptomatically in adults, its occurrence within the first 2 months in infants, who cannot generate their own antibodies, leads to serious morbidity and mortality (1). Coughing fits, sensation of inspiratory suffocation, and post-coughing vomiting are classic symptoms in unvaccinated children under 10 years old (2). Information regarding pertussis during pregnancy is limited. We wanted to raise awareness on this issue by sharing our clinical approach to managing a pregnant patient diagnosed with pertussis in the third trimester.

A 22-year-old primigravida at 36 weeks and 4 days of an uncomplicated antenatal follow-up presented with increasing nocturnal cough complaints. The patient did not report fever, chills, or shivering. Considering the predominant symptoms as suggestive of atypical upper respiratory tract infection (URTI), the patient was started on cephalosporin and bronchodilator therapy. As the patient did not show improvement after one week of treatment and her general condition deteriorated, she was planned for hospitalization. Bordetella pertussis positivity was detected in the respiratory panel test conducted at this stage. Azithromycin was added to the treatment, and droplet isolation was initiated. Active labor began spontaneously 22 days after the onset of symptoms (at 39 weeks and 5 days), and a cesarean section was performed due to breech presentation. To protect the baby, breastfeeding with a mask was recommended, and both the mother and the baby were discharged on postoperative day 2. No illness was detected in the newborn during follow-up.

In a previous study, it was reported that both symptoms (cough, post-cough vomiting) and the need for hospitalization were similar in pregnant and non-pregnant individuals. The study also emphasized that half of the cases were diagnosed in the third trimester. When the babies of 30 patients diagnosed in the third trimester were examined, a perinatal transmission rate of 10% (n=3/30) was found. In summary, there is evidence that pertussis contracted during pregnancy does not increase maternal and fetal complications (3).

Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for tetanus, diphtheria, and pertussis. Infants and young children are recommended to receive a 5-dose series of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines, with one adolescent booster dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. Adults who have never received Tdap also are recommended to receive a booster dose of Tdap. Women are recommended to receive a dose of Tdap during each pregnancy, which should be administered from 27 through 36 weeks' gestation, regardless of previous receipt of Tdap. After receipt of Tdap, adolescents and adults are recommended to receive a booster tetanus and diphtheria toxoids (Td) vaccine every 10 years to assure ongoing protection against tetanus and diphtheria (4, 5).

In a meta-analysis that was conducted, in infants of Tdap-immunized women, two-fold higher levels of anti-pertussis toxin (PT) and anti-diphtheria-toxoid (DT) IgG pre-primary immunization were associated with 9% and 10% lower post-primary immunization levels (6).

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Sorumlu Yazar/Corresponding Author: Nizamettin BOZBAY, Department of Perinatology, Selcuk University Faculty of Medicine, 42130 Selçuklu/Konya, Türkiye
E-mail: dr.nizamettin.bozbay@gmail.com

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Vaccines containing pertussis have been safely used in many countries for many years. The efficacy of pertussis vaccines is reported to be over 90% (7, 8). In our country, pertussis vaccines are routinely administered in childhood, but routine pertussis vaccination is not performed in pregnant women. In Turkey, the Ministry of Health administers Td vaccine starting from the second trimester as at least 2 doses in the vaccine program.

While there are many strategies to prevent pertussis in early infancy, the most appropriate and cost-effective is undoubtedly maternal vaccination. We believe that administering the pertussis vaccine after the second trimester can increase newborn immunity rates. Additionally, vaccination in early pregnancy can reduce the risk of maternal disease development.

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OLGU SUNUMU / CASE REPORT

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Prenatal findings and postnatal confirmed of perlman syndrome: a case report

Perlman sendromu: Prenatal ve postnatal bulgular

Erdal ŞEKER[1], Mehmet Seçkin ÖZIŞIK[1], Elvis KRAJA[2], Yasemin Ezgi KÖSTEKÇİ[2], Emel OKULU[2], Acar KOÇ[1]

[1]Department of Obstetrics and Gynaecology, Ankara University School of Medicine, Ankara, Türkiye
[2]Department of Neonatology, Ankara University School of Medicine, Ankara, Türkiye

ABSTRACT

Perlman syndrome is an extremely rare syndrome characterized by polyhydramnios, fetal overgrowth, facial dysmorphism and visceromegaly, and inherited in an autosomal recessive fashion. We here report a male infant born to consanguineous parents with prenatal history of polyhydramnios, fetal ascites, nephromegaly, corpus callosum agenesis and choroid plexus cysts, and presented with nephromegaly, hepatomegaly, cholestasis, cardiomegaly, cryptorchidism, respiratory distress, hypoglycemia, generalized muscle hypotonia after birth, and died due to progressive respiratory decompensation at the age of 6 months. He was diagnosed with Perlman syndrome (#267000) confirmed with a homozygous variant mutation in the DIS3L2 gene.

Keywords: Perlman syndrome, nephromegaly, polyhydramnios, fetal ascites, DIS3L2 gene

ÖZ

Perlman sendromu, polihidramnios, fetal aşırı büyüme, yüz dismorfizmi ve visseromegali ile karakterize edilen ve otozomal resesif olarak kalıtılan son derece nadir bir sendromdur. Bu vakamızda, akraba evliliği yapmış ebeveynlerden doğan bir erkek bebeği bildirmekteyiz. Doğum öncesi dönemde polihidramnios, fetal asit, nefromegali, korpus kallozum agenezisi ve koroid pleksus kistleri öyküsü bulunan bebek, doğum sonrası nefromegali, hepatomegali, kolestaz, kardiyomegali, inmemiş testis, solunum sıkıntısı, hipoglisemi, genel kas hipotonisi ortaya çıktı ve 6 aylıkken ilerleyici solunum yetmezliği nedeniyle hayatını kaybetti. DIS3L2 geninde homozigot varyant mutasyonu ile Perlman sendromu (#267000) teşhisi doğrulandı.

Anahtar Kelimeler: Perlman sendromu, nefromegali, polihidramnios, fetal asit, DIS3L2 geni

INTRODUCTION

Perlman syndrome is a rare autosomal recessively inherited syndrome characterized by overgrowth of the body or body parts and is seen with a frequency of 1/1,000,000. It shows autosomal recessive inheritance. Homozygote or compound heterozygous mutations in the DIS3 like 3'-5' exoribonuclease 2 genes (DIS3L2, 614184) have been identified in patients with Perlman syndrome by Astuti et al. (1). So far, 39 cases have been described in the literature (2-5).

The characteristic features of renal morphology were described by Liban and Kozenitsky, but the first clinical cases in the literature who were siblings and born by consanguineous parents were described by Perlman (6-10). Neri et al. designated the syndrome and proposed the name, Perlman (10). Additional patients have been described since that time until today.

Alessandri et al. summarized the clinical features of all 28 patients reported in the literature in the whole world (11). Prenatal ultrasonography (USG) showed macrosomia, polyhydramnios, and nephromegaly. The postnatal clinic was marked by large for gestational (LGA; Birth weight more than 90th percentile) macrocephaly, dysmorphic facial features like a depressed broad nasal bridge with a short nose, long anteverted and inverted V-shaped upper lip, micro-retrognathia, deep-set eyes with epicanthic fold, low-set ears, round facial fullness and upsweep of anterior scalp hair, abdominal distention and visceromegaly mainly nephromegaly and hepatomegaly, cardiovascular anomalies, central nervous system (CNS) anomalies, hypotonia, developmental delay, and intellectual disability.

Histological examination shows nephroblastomatosis (75%) and pancreatic cell hyperplasia (71%) in patients (11, 12). Predisposition to renal hamartoma, nephroblastoma known as Wilms' tumor (WT)

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Sorumlu Yazar/Corresponding Author: Erdal ŞEKER, Ankara Üniversitesi Tıp Fakültesi Hastanesi, 06100 Mamak/Ankara, Türkiye
E-mail: erdalseker84@gmail.com

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has been reported. The average developing age for WT in Perlman syndrome is <2 years old and is lower than sporadic WT cases which develop at 4 years old children and renal cell carcinoma is seen in long-term follow-up.

Prognosis is severe with high mortality where half of them die in the neonatal period (<28 days) and only some patients (19%) have been reported to survive. This high neonatal mortality occurs due to respiratory problems like pulmonary hypoplasia and hypoxemia or other systemic problems like hypoglycemia and renal failure. (3) A long life span has been reported in some cases. A 9-years-old patient who had a normal neurodevelopmental outcome was reported by Piccione, and a 34-years-old patient who survived with mild psychomotor delay (12, 13).

The differential diagnosis of other overgrowth syndromes, especially Beckwith–Wiedemann syndrome (BWS) and Simpson–Golabi–Behmel syndrome (SGBS), Weaver and Sotos are difficult to distinguish from Perlman syndrome. Macroglossia and exomphalos presented in BWS and polydactyly presented in SGBS are absent in Perlman. Genetic testing should be considered.

We here presented a case that prenatally described to have nephromegaly, bilateral choroid plexus cyst (CPC), partial agenesis of the corpus callosum, and ascites and postnatally diagnosed as Perlman syndrome with clinical features and genetic testing.

CASE PRESENTATION

The male infant was the fourth, but the second alive child of consanguineous parents. The previous pregnancies had resulted in infants of which one antenatally diagnosed bilateral hydronephrosis and died at the third day of life with an, and the other died at 3-months old due to aspiration syndrome. One sibling who is 18-months old is healthy. The 27-year-old mother reported no medical problems, exposure to teratogens or alcohol. She was referred to our perinatal center at 18 weeks of gestation. At 22 weeks of gestation, a detailed ultrasound examination showed enlarged kidneys (29,26*40,92 mm) (Abonyi 2019), pericardial effusion choroid plexus cyst, and partial agenesis of corpus callosum (PACC). (Figure 1 and Figure 2) Amniocentesis revealed a normal karyotype (46, XY).

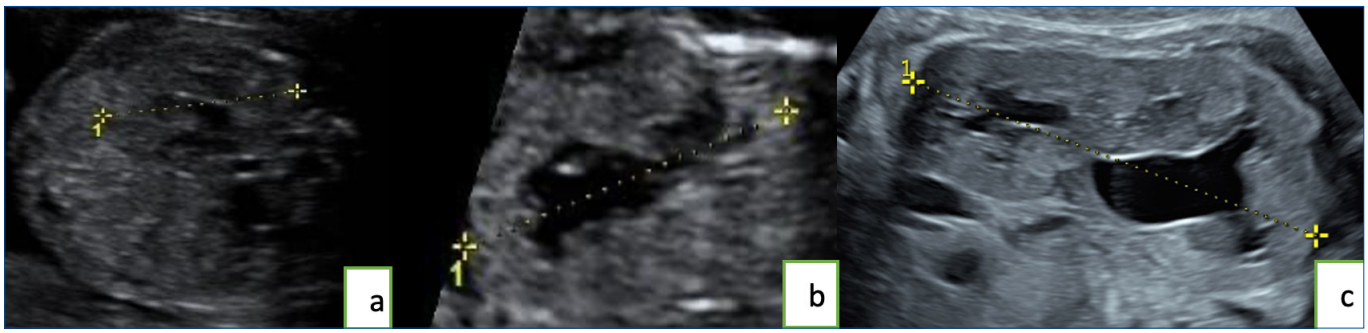

Figure 1. Prenatal renal meassurment. **a:** 29 mm (length) and **b:**40 mm (width) (22 w 6 day). **c:**78 mm (length) (34 w 2 day)

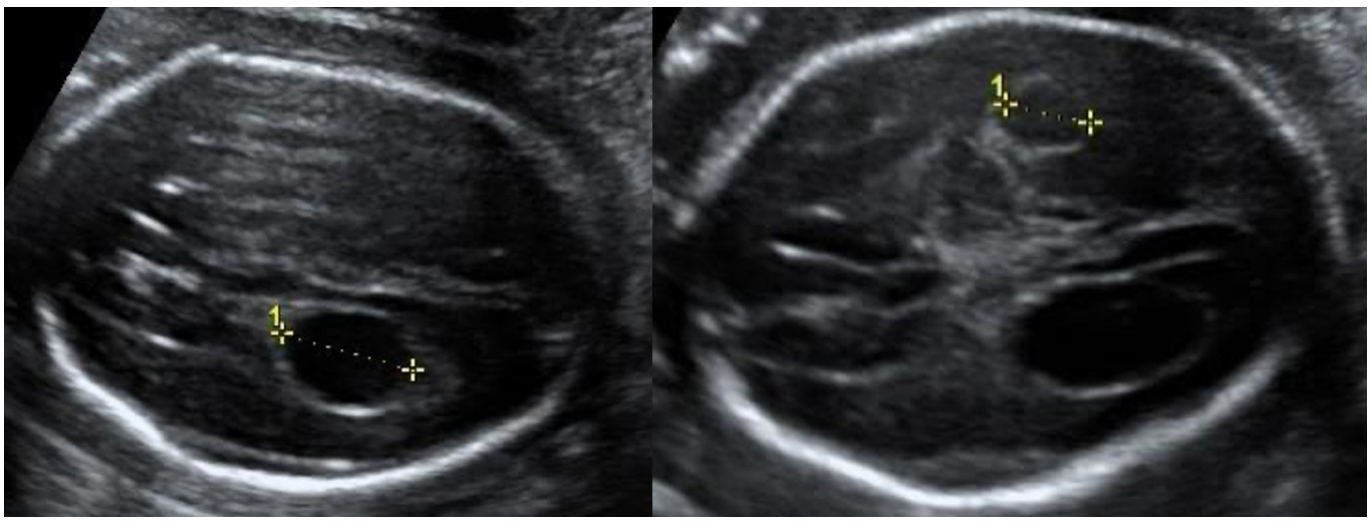

Figure 2. 17,06 mm and 9,93 mm CPC. (22 w6 d)

CPC: Choroid plexus cyst

Figure 3. Postnatal view of the neonatal baby.

The baby was born at 38 weeks of gestation by cesarean section with a birth weight of 3850 g, a length of 47 cm, and a head circumference of cm. Apgar scores were 5 and 6 at the 1th and 5th minutes, respectively. He received nasal continuous positive airway pressure (nCPAP) after birth, then intubated at following hours. He had marked abdominal distention and enlarged kidneys were palpated. Facial anomalies included depressed nasal bridge, prominent forehead, deep-set eyes, low-set ears, high arched palate (Figure 3). Renal ultrasonography showed enlarged and hyperechogenic kidneys (left: 105x55x50 mm, right: 102x50x48 mm) with small cystic lesions, a pattern indistinguishable from polycystic kidney disease. The graphics of the skeleton were normal. Echocardiography showed a secundum atrial defect. MR imaging was performed at which the lateral ventricle appears dilated and the CC was thin.

He received phototherapy due to jaundice on the 2nd day of his life. There was neither rhesus nor blood group incompatibility. On the 5th day of his life, an exchange transfusion was performed due to indirect hyperbilirubinemia (29.7 mg/dL). The direct bilirubin level was 2.5 mg/dL and increased gradually. The evaluations for cholestasis were all normal (viral serology, thyroid function test, metabolic test, liver ultrasound). UDCA treatment was started at a dose of 10 mg/kg/d. Cholestasis resolved in 6 weeks.

We identified a homozygous deletion of exon 9 in the DIS3L2 gene in our patient. Both mother and father were heterozygous for this mutation (HGMD ID: CG1312724/CG121615).

The infant was transferred back to a lower-level care nursery close to the family's home at the age of 3-months. We learned that he died at the age of 6 months due to progressive respiratory decompensation and sepsis.

DISCUSSION

Perlman syndrome is a rare syndrome characterized by visceromegaly, renal lesion, and high neonatal mortality. The first cases were described by Liban and Kozenitzky in 1970 in two siblings (6). Later, three siblings in the same family were identified by Perlman (8, 9). Multiple metanephric hamartomas and nephroblastomatosis were reported in male neonates, and, and diffuse-type WT was described in their sister. Patients reported having features as typical facial appearance, protruding forehead, flattened nose, V-shaped flat-wide upper lip. Until 2012, the genetic basis of Perlman syndrome was unknown. In 2012, Astuti et al. identified the Perlman syndrome and the cancers that may be caused by Perlman syndrome (1). They defined 2q37.1 as chromosome and region and DIS3L2 as gene mutation. They claimed that the genetic cause of Perlman syndrome would also lead to other cancer-causing causes. To our knowledge, this is the first case report from our country that has prenatally described features and diagnosed as Perlman syndrome with postnatal features which was confirmed as genetically in both infant and his parents.

Perlman syndrome has a poor prognosis. In a review, 11 of 28 patients lived until 1-year-old. The vast majority of patients died

from respiratory distress syndrome, sepsis, and kidney failure. WT developed in 7 of 11 patients who survived (11). The case presented by Piccone had a normal neurodevelopmental outcome (12). Although the genetic cause of Perlman syndrome has been elucidated, the clinical variability between cases is unknown.

Unlike other findings, the presented case had CPC that we detected during early pregnancy. Other nephromegaly and visceromegaly syndrome were considered in the differential diagnosis. But the absence of macroglossia, abnormal tongue structure or hemi hyperplasia distanced us from the diagnosis of BWS. The absence of polydactyly, lip, and palate problems led us to exclude the diagnosis of Simpson-Golabi-Behmel syndrome.

There are many reported antenatal USG findings of Perlman syndrome. Deroche et al. reported a fetus with lymphedema, dextrocardia, placentomegaly detected at 18. gestation weeks with elevated α-fetoprotein and human chorionic gonadotropin (14). They found intracranial hemorrhage, sinus venous thrombosis, and peripheral calcification in sella turcica in the neonatal period. Activated C protein resistance was detected in thrombophilia tests. The difference between this case from our case and other literature cases is still unknown.

Unlike other cases reported in the literature, our patient did not have macrosomia as described by Demirel et al. (15). Hyperbilirubinemia and jaundice were also detected in our patient. The cause of hyperbilirubinemia in these cases is still unclear.

CONCLUSION

The management of Perlman syndrome includes a multidisciplinary team of specialists according to features observed in patients. Genetic counseling and prenatal genetic diagnosis should be offered in the next pregnancy. A quick diagnosis and accurate follow-up are needed for these patients to give support to high rates of morbidities and mortality. Infants should be followed up for possible malignancies. Gene therapy can be the future focus in Perlman syndrome.

Conflict of interest

The authors report no conflicts of interest.

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This article has not been previously published and has not been posted elsewhere at the same time.

Written informed consent was obtained from the patient.

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