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Prematüre Bebeklerde Trombositopeni ile Ciddi Prematüre Retinopatisi Arasındaki İlişkinin Değerlendirilmesi

Evaluation of The Relationship Between Thrombocytopenia and Severe Retinopathy of Prematurity

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ÖZ

Amaç: Prematüre bebeklerde tedavi gerektiren ciddi prematüre retinopatisi (ROP) gelişiminde trombositopeni varlığının prediktif değerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: 2015-2019 yıllarında 240/7-296/7 gestasyon hafta arasında tek bir merkezde doğan bebekler retrospektif olarak değerlendirildi. Postkonsepsiyonel <30 hafta öncesi en düşük trombosit değeri ve diğer neonatal veriler hasta kayıtlarından alındı. Trombosit değerinin <150.000 /L olması trombositopeni olarak kabul edildi. Postnatal 4-6. haftadan itibaren 1-2 hafta aralıklarla yapılan retina muayene sonuçları değerlendirildi. Çalışma popülasyonu; ROP yok veya hafif ROP ve ciddi ROP olarak 2 gruba ayrıldı. Elde edilen veriler gruplar arasında karşılaştırıldı.

Bulgular: 656 bebeğin verileri incelendi. Çalışma grubunun ortalama gebelik haftası ve doğum ağırlığı sırasıyla 27,3±1,4(24-29) hafta, 940±228(560-1280) g idi. Tedavi gerektiren ciddi ROP 52(%7,9) hastada vardı. Ciddi ROP grubunda diğer gruba göre gebelik haftası (ve doğum ağırlığı anlamlı düzeyde düşüktü. (p<0,001) Ciddi ROP grubunda trombositopeni daha sık bulundu (%41,2 vs 15,8; p<0,001). Respiratuar distres sendromu (RDS) (p=0,04), geç neonatal sepsis (p=0,048), evre3-4 intraventriküler kanama (p<0,001), orta-ağır bronkopulmoner displazi (p<0,001), hemodinamik anlamlı patent duktus arteriozus (p<0,001) ciddi ROP grubunda daha fazlaydı. Ayrıca ciddi ROP grubunda mekanik ventilasyon gereksinimi daha sık (p<0,001) ve tam enteral beslenmeye geçiş süresi (p<0,001) de daha uzun bulundu. Lojistik regresyon analizi yapıldığında; tedavi gerektiren ciddi ROP için <28 gebelik haftası (OR 4.38, 95% CI 2.18-8.78; p<0,001), mekanik ventilasyon gereksinimi (OR 4.89, 95% CI 2.59-9.22;p<0,001) ve trombositopeninin (OR 2.49, 95% CI 1.28-4.83;p=0,007) bağımsız risk faktörleri olduğu görüldü.

Sonuç: Postkonsepsiyonel <30 hafta öncesi trombositopeni ciddi ROP gelişimi açısından önemli bir risk faktörüdür. Prematüre bebeklerde normal retinal vasküler gelişimi için proanjiogenik etkileride olan trombositlerin etkinliği de göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Prematüre, ROP, Trombositopeni

ABSTRACT

Aim: It was aimed to examine the predictive value of the presence of thrombocytopenia in the development of severe retinopathy of prematurity (ROP) requiring treatment in premature infants.

Material and Methods: babies born in a single center between 24 0/7-29 6/7 weeks of gestation in 2015-2019 were evaluated retrospectively. The lowest platelet counts before postconceptional <30 weeks and other neonatal data were obtained from patient records. Thrombocytopenia was defined as a platelet value of <150,000/L. Retinal examination results, which were performed at 1-2 week intervals from postnatal 4-6. weeks, were evaluated. Study population were divided into 2 groups as no ROP or mild ROP and severe ROP.

Results: Data of 656 infants were analyzed. The mean gestational week and birth weight of the study group were 27,3±1,4(24-29) weeks, 940±228(560-1280) g, respectively. Severe ROP requiring treatment was present in 52(7,9%) patients. Gestational week and birth weight were significantly lower in the severe ROP group compared to the other group (p<0,001). Thrombocytopenia was found more frequently in the severe ROP group (41,2% vs 15,8%; p<0,001). Respiratory distress syndrome (p=0,004), late neonatal sepsis(p=0,048), stage3-4 intraventricular hemorrhage (p<0,001), moderate-severe bronchopulmonary dysplasia(p<0,001), hemodynamically significant patent ductus arteriosus(p<0,001) was higher in the severe ROP group. In addition, the need for mechanical ventilation was found to be more frequent(p<0,001) and the transition time to full enteral feeding(p<0,001) was found to be longer in the severe ROP group. When logistic regression analysis is done; For severe ROP requiring treatment, <28 weeks of gestation (OR 4.38, 95% CI 2.18-8.78; p<0,001), mechanical ventilation requirement (OR 4.89, 95% CI 2.59-9.22; p<0,001) and thrombocytopenia (OR 2.49, 95) %CI 1.28-4.83; p=0,007) were found to be independent risk factors.

Conclusion: Thrombocytopenia before <30 weeks postconceptional is an important risk factor for the development of severe ROP. The efficacy of platelets, which also have proangiogenic effects, should also be considered for normal retinal vascular development in premature infants.

Keywords: Prematurity, ROP, Thrombocytopenia

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GİRİŞ

Prematüre retinopatisi (ROP), prematüre bebeklerin tam olarak vaskülarize olmayan retinasında gelişen multifaktöriyel vazoproliferatif bir hastalıktır. ROP, dünyadaki tüm çocukluk çağı körlüklerinin yaklaşık %40'ını oluşturan çok önemli bir hastalıktır. Yenidoğan bakımı geliştikçe, düşük doğum ağırlıklı bebeklerin hayatta kalma oranı artmakta ve sonuç olarak ROP insidansı artmaktadır (1, 2). İmmatürite ve aşırı oksijen uygulaması ROP için belirlenen başlıca risk faktörleridir. Bunların yanında ROP ile respiratuar distres sendromu (RDS), bronkopulmoner displazi (BPD), anemi, trombositopeni, kan transfüzyonu, patent duktus arteriyozus (PDA), nekrotizan enterokolit (NEK), bakteriyel ve fungal sepsis ve intraventriküler kanama (İVK) gibi komorbiditeler arasındaki ilişki de araştırılmıştır (3).

Anjiyogenez, ROP'un patolojik sürecinde anahtar bir rol oynar ve pro- ve antianjiyojenik faktörlerin salınımı ile düzenlenir. OP patogenezinin iki fazdan oluştuğu düşünülmektedir. Birinci faz, doğum sonrası hiperoksiye yanıt olarak damarlarda vasküler endotelyal büyüme faktörü (VEGF) ve insülin benzeri büyüme faktörü-1 (IGF-1) dahil anjiyojenik faktörlerin azalmasına ikincil vazo-obliterasyonu içerir. Avasküler retinanın metabolik taleplerinin artışına bağlı olarak gelişen retinal hipoksi, VEGF düzeylerinin yükselmesine yol açar ve bunun sonucunda ilk olarak 30-32 haftalık postmenstrüel yaşta (PMA) tespit edilebilen vazoproliferasyon ikinci fazı oluşur yada ortaya çıkar (4).

Trombositlerin, hemostaz dışında anjiyojenezin düzenlenmesini de içeren fonksiyonları vardır; trombositler ve megakaryositler hem pro- hem de antianjiyogenik mediatörleri α-granüllerinde depolar. Trombositler, VEGF), IGF-1) ve trombosit kaynaklı büyüme faktörü (PDGF) gibi anjiyogenezin farklı anahtar düzenleyicilerini biriktirir, taşır ve iletir (5). VEGF vasküler endotelyal hücre proliferasyonuna katkıda bulunan proanjiyojenik faktörlerden biridir ve ROP patogenezinde kritik bir role sahiptir. Trombositlerin patolojik retina neovaskülarizasyonundaki sınırlayıcı etkisi de bildirilmiştir (6–7). Trombositopeni erken doğmuş bebeklerde sık görülür (8, 9) ve sıklıkla sepsis ve nekrotizan enterokolit (NEK) ile ilişkilidir (10, 11). Bir vaka raporu, proliferatif ROP sırasında trombosit transfüzyonunun neovaskülarizasyonu (NV) engelleyebileceğini düşündürmektedir (12). Bazı çalışmalarda (13,14), trombositopeninin şiddetli ROP ile anlamlı şekilde ilişkili olduğu bulunmuştur. Bununla birlikte, trombositopeni ile şiddetli ROP arasındaki genel ilişki henüz araştırılmamıştır.

Bu çalışmada, prematüre bebeklerde tedavi gerektiren ciddi ROP) gelişimi için trombositopeni varlığının prediktif değerinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEMLER

2015-2019 yıllarında 240/7-296/7 gestasyon hafta arasında tek bir merkezde doğan bebekler retrospektif olarak değerlendirildi. Çalışmaya postnatal 4-6. haftadan başlayarak en az 43 haftaya kadar ROP muayeneleri yapılmış olan bebekler çalışmaya dahil edildi. Takipleri düzenli olmayan ve dosyalarında muayene bilgileri eksik olan prematüre bebekler çalışma dışı bırakıldı. Hastaların demografik verileri, postkonsepsiyonel 30 hafta öncesi en düşük trombosit değeri, diğer neonatal klinik veriler ve eşlik eden prematürite ilişkili komorbiditeler (RDS, geç neonatal sepsis, BPD, İVK, PDA, NEK) elektronik tıbbi kayıtlardan elde edildi. Trombosit değerinin <150.000 /L olması trombositopeni olarak kabul edildi. ROP taraması, tarama kılavuzlarına göre postnatal 4 haftalıkken veya PMA 31 haftalıkken deneyimli bir oftalmolog tarafından indirekt oftalmoskop kullanılarak yapıldı (15). Postnatal yaş 43 haftaya ulaşana kadar ve/veya retinal vaskülarizasyon ora serrataya 360° ulaşana kadar takip muayeneleri yapıldı. Takip aralıkları ROP şiddetine göre planlandı. Pupil dilatasyonu için %2.5 fenilefrin ve %0.5 tropikamid kullanıldı. Fundus muayenesi indirekt oftalmoskop ve 28D lens kullanılarak yapıldı. Fundus bulguları kaydedildi. ROP tanısı ve evrelemesi, Uluslararası ROP Sınıflandırma Komitesi'nin (ICROP) kılavuzlarına göre belirlendi (16). Tedavi kararlarında ROP için Erken Tedavi (ETROP) deneme kriterleri (tip-1 ROP kriterleri) kullanıldı. Buna göre; Zon-I, artı hastalıklı herhangi bir evre ROP; artı hastalığı olan veya olmayan bölge-I, evre-3 ROP; ve Zon-II, Evre-2 veya 3 artı hastalıklı tedavi endikasyonu olarak kabul edildi (17). Çalışma populasyonu; ROP yok veya hafif ROP ve ciddi ROP (lazer fotokoagülasyon veya intravitreal anti-VEGF enjeksiyonu uygulanan bebekler) olarak 2 gruba ayrıldı. Elde edilen veriler gruplar arasında karşılaştırıldı.

İstatistiksel analizler için Microsoft Windows için SPSS IBM version 22.0 kullanıldı. Verilerin dağılımını belirlemek için Shapiro-Wilk normallik testi uygulandı. Normal dağılmayan veriler medyan (min-maks), normal dağılan veriler ortalama±standart sapma (SS) olarak ifade edildi. Normal dağılıp dağılmadığına göre veriler Student T-test veya Mann Whitney U test kullanılarak analiz edildi. Kategorik verilerin analizinde Ki-kare testi kullanıldı. p değeri <0,05 istatistiksel olarak anlamlı kabul edildi. Ciddi ROP için bağımsız risk faktörlerini değerlendirmek amacıyla logistik regresyon analizi yapıldı.

BULGULAR

Toplam 656 bebeğin verileri incelendi. Çalışma grubunun ortalama GH ve DA sırasıyla 27,3±1,4 (24-29) hafta, 940±228 (560-1280) g idi. Tedavi gerektiren ciddi ROP 52 (%7,9) hastada saptandı.

Tablo 1. Bebeklerin demografik özellikleri

	ROP yok/Hafif ROP (n=604)	Ciddi ROP (n=52)	p
Gebelik haftası, hafta*	28 (24-29)	26 (25-29)	0,001
Doğum ağırlığı, g*	1080 (450-1500)	850 (560-1280)	0,001
Erkek, n%	311(51,5)	23 (44,2)	0,38
Sezaryen, n%	502 (83,1)	38 (73,1)	0,08
Preeklampsi, n%	106 (17,9)	13 (25)	0,19
EMR, n% **Antenatal steroid, n%**	125 (20,7) 406 (67,2)	12 (23,1) 35 (67,3)	0,72 0,99
APGAR-5. dk*	8 (3-10)	7 (2-9)	0,013
SGA, n % **Çoğul gebelik, n %** **Gestasyonel diyabet, n%**	72 (12,1) 135 (22,4) 24 (4)	7 (13,5) 11(21,2) 2 (3,8)	0,82 0,98 0,99
Histolojik koryoamniyonit, n%	89 (14,7)	12 (23,1)	0,11

*Median (min-maks). EMR: Erken membran rüptürü; SGA: Small for gestational age

Ciddi ROP grubunda diğer gruba göre GH ve DA anlamlı düzeyde düşüktü. (p<0,001) Diğer demografik özellikler açısından gruplar arasında anlamlı fark yoktu. (Tablo 1) Ciddi ROP grubunda trombositopeni sıklığı daha fazla idi. (%41,2 vs 15,8; p<0,001). RDS) (%75 vs %55,3; p=0,004), geç neonatal sepsis (GNS) (%38,5 vs 25,3; p=0,048), evre3-4 intraventriküler kanama (İVK) (%26,9 vs %7; p<0,001), orta-ağır bronkopulmoner displazi (BPD) (%42,3 vs %9,8; p<0,001), hemodinamik anlamlı patent duktus arteriozus (PDA) (%63,5 vs %39,1; p<0,001) ciddi ROP grubunda daha fazlaydı. Ayrıca ciddi ROP grubunda mekanik ventilasyon gereksinimi daha sık (%55,8 vs %14,9; p<0,001) ve tam enteral beslenmeye geçiş süresi(p<0,001) de daha uzun bulundu. (Tablo 2) Lojistik regresyon analizi yapıldığında; tedavi gerektiren ciddi ROP için <28 GH (OR 4.38, 95% CI 2.18-8.78 (p<0,001), mekanik ventilasyon gereksinimi (OR 4.89, 95% CI 2.59-9.22; p<0,001) ve trombositopeninin (OR 2.49, 95% CI 1.28-4.83; p=0,007) bağımsız risk faktörleri olduğu görüldü.

TARTIŞMA

ROP insidansı, farklı sosyoekonomik gelişmeler, çalışma tasarımlarındaki ve sağkalım oranlarındaki değişkenlik nedeniyle ülkeler arasında değişmektedir. Mevcut çalışmada, genel ROP insidansı %34,3 iken, bebeklerin %7,9'unda ciddi ROP kaydedilmiştir. Bu sonuçlar gelişmekte olan ülkelerin oranlarına benzerdi (18,19,20).

Gelişmekte olan ülkelerde, daha yüksek GH ve DA'ya sahip bebekler ROP gelişimi için risk altındadır (21,22). Ülkemizden yakın zamanda yapılan bir ROP çalışması sonuçlarına göre GH ≤34 hafta veya DA <1.700 g olan bebeklerde ROP taraması yapılması önerilmiştir (23). Mevcut çalışmamızda da küçük GH, mekanik ventilasyon gereksinimi ve doğumdan sonraki ilk haftadaki düşük trombosit sayısı ROP ilerlemesi için bağımsız risk faktörleri olarak ortaya çıktı.

Tablo 2. Bebeklerin klinik sonuçları

	ROP yok/Hafif ROP (n=604)	Ciddi ROP (n=52)	p
Respiratuvar distres sendromu, n%	334 (55,3)	39 (75)	0,004
Patent duktus arteriozus, n%	236 (39,1)	33 (63,5)	0,001
Erken neonatal sepsis, n%	97 (16,1)	7 (13,5)	0,84
Geç neonatal sepsis, n%	153 (25,3)	22 (38,5)	0,048
İntraventriküler kanama evre 3-4, n%	42 (7)	14 (26,9)	0,001
Mekanik ventilasyon gereksinimi,n%	90 (14,9)	29 (55,8)	0,001
Bronkopulmoner displazi orta-ağır, n%	58 (9,8)	22 (42,3)	0,001
Mortalite, n%	47 (7,8)	3 (5,8)	0,78
Tam enteral beslenmeye geçiş süresi, gün*	14 (7-54)	18 (11-56)	0,001
Beslenme intoleransı, n%	224 (39)	28 (53,8)	0,040
Trombositopeni, n%	90 (15,8)	21 (41,2)	0,001

*Median (min-maks)

Retinanın savunmasız yapısı göz önüne alındığında hem düşük GH hem de düşük DA, doğumda eksik vasküler ve retinal nöral gelişim ile ilişkilidir (24). Çalışmamızda lojistik regresyona göre GH, şiddetli ROP gelişimi için bağımsız risk faktörü olarak bulundu. Bununla birlikte DA, ciddi ROP risk faktörü olarak bulunmadı. Bu sonucun ciddi ROP olan hasta sayısının az oluşuna bağlı olduğu düşünüldü.

Vinekar ve ark. (12), serum trombosit transfüzyonlarından sonra gerileyen ciddi trombositopenili agresif posterior ROP olgusunu sunmuşlardır. Jensen ve ark. (7) zon 1 olgularda trombositopeni ile tip 1 ROP varlığı arasında ilişki olduğunu göstermişlerdir. Bu çalışmaların sonuçları trombositopeninin zon 1 ROP için bir risk faktörü olduğunu düşündürmektedir. Çakır ve ark. (25), bir fare ROP modelinde ≥30 haftalık postmenstrüel yaştaki herhangi bir trombositopeni epizodunun şiddetli ROP ile ilişkili olduğunu göstermiştir. Araştırmacılar, farelerin haftalık ortalama trombosit sayısını değerlendirmişler ve şiddetli ROP grubu ile şiddetli ROP'u olmayan veya daha az şiddetli ROP grubu arasında istatistiksel olarak anlamlı bir fark bulmuşlardır. Jensen ve ark.(7) ise PMA'nın doğumdan 34. haftasına kadar olan trombositopeninin ciddi ROP ile ilişkili olduğunu göstermişlerdir. Bizde çalışmamızda , literatür ile uyumlu olarak prematüre bebeklerde düşük trombosit sayısının ROP gelişimi için bir risk faktörü olduğunu bulduk.

Yapılan çalışmalarda bazı pro- ve anti-anjiyojenik düzenleyicinin trombositlerde biriktiği ve taşındığı gösterilmiştir (7,12). Trombosit alfa granüllerinin içerdiği IGF-1, IGF-bağlayıcı protein 3 (IGF-1 için birincil serum bağlayıcı protein), VEGF, ve trombosit kaynaklı büyüme faktörü (PDGF) ile IGF-1 ve VEGF seviyeleri ROP gelişimi için kritik öneme sahiptir (26). Buna göre, düşük trombosit sayısının ROP gelişimine yol açmasını sağlayan mekanizma IGF-1'in trombositler tarafından sağlanması olabilir. VEGF kaynaklı damar büyümesi için IGF-1 gerekliyken, erken gebelik haftasında düşük trombosit sayısına bağlı yetersiz IGF-1 sunumu nedeniyle retinal vaskülogenez yavaşlar ve ardından tip 1 ROP gelişir.

ROP, iç retinada ve preretinal boşlukta patolojik anjiyogenez ile seyreden bir hastalıktır (27). Yeni oluşan kan damarları olgun değildir ve bu da vasküler sızıntıya yol açabilir (27). Perisitler, endotelyal hücreler için hayatta kalma sinyallerine katkıda bulunarak anjiyogenezde çok önemli bir role sahiptir (28). PDGF, perisit canlılığı için gereklidir (29). Ayrıca PDGF, endotel hücrelerinin hem çoğalması hem de göçü için esastır (29). Perisit eksikliği, endotel hiperplazisi, genişlemiş kılcal damarlar, düzensiz şekilli endotel hücreleri ve artmış transendotelyal geçirgenlik ile bağlantılıdır (29). Hammes ve ark. (30), PDGF eksikliği olan farelerin, büyüyen retinanın erken doğum sonrası fazında vahşi tip farelere kıyasla daha az perisite sahip olduğunu göstermiştir. Perisitler muhtemelen endotel hücre sağkalımını teşvik etmede ve endotel hiperplazisini sınırlamada bir role sahiptir. Buna göre, düşük trombosit sayısı ile ROP gelişimini birbirine bağlayan ikinci yol, PDGF eksikliğidir. Sonuçlarımız ve literatürden elde edilen veriler, yüksek VEGF seviyelerinde (örn, ROP), düşük dolaşımdaki PDGF seviyelerine (örn. trombositopeni) bağlı perisit kaplama eksikliğinin, artmış bir neovasküler cevaba yol açabileceğini düşündürmektedir.

ROP modellerinde, yenidoğan sıçanların retinalarına hiperoksi oluşturulması VEGF düzeylerini düşürür ve retinal anjiyogenezi zayıflatır (31,32). İkinci hafta boyunca oda havasının relatif hipoksisi, VEGF sentezinin artmasına ve patolojik anjiyogenezin artmasına yol açar (33). ROP'un bu proliferatif fazı sırasında, VEGF seviyeleri lokal ve sistemik olarak yükselir (34).

VEGF, hipoksi sonrası endotel hücre göçünü ve proliferasyonunu indükler (34). Bu dönemde trombositopeni, perisit canlılığı için gerekli olan PDGF eksikliğini derinleştirebilir. PDGF eksikliği patolojik anjiyogenez ile sonuçlanabilir.

Çalışmamızdaki çalışma grubu, bölge 1 ve bölge 2'de sınıflandırılan tüm ROP vakalarını içermektedir. Trombosit sayıları trombositopeni düzeyine ulaşmamasına rağmen ROP geliştiren ve geliştirmeyen bebekler arasında trombositopeni yüzdesi bakımından anlamlı bir fark vardı. Trombositler, trombositler tarafından depolanan, taşınan ve dağıtılan VEGF ve PDGF gibi anjiyojenik düzenleyici proteinlerin ana düzenleyicileridir (5). Bu durumun ROP patogenezinde rol oynadığı düşünülmektedir. Bulgularımız dolaşımdaki trombosit sayısı ve buna bağlı olarak trombositler tarafından taşınan anjiojenik düzenleyici protein düzeyinde azalmanın retinal vasküler olgunlaşma ve rOP gelişim üzerine olumsuz etkilerinin olduğunu düşündürmektedir.

Doğum sonrası kilo alımının ROP gelişimi üzerine etkisi ile ilgili fazla sayıda çalışma yapılmıştır (4,5). Çalışmamızda postnatal kilo alımı ile ilgili veri paylaşılamamakla birlikte bu da çalışmamızın kısıtlılıklarından biridir. Sonuç olarak, Prematüre bebeklerde normal retinal vasküler gelişimi için pro-anjiogenik etkileride olan trombositlerin etkinliği de göz önünde bulundurulmalıdır. Trombositopeni ve ROP arasındaki potansiyel ilişkiyi tanımlamak için daha geniş ölçekli ileriye dönük çalışmalara ihtiyaç vardır.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Early Second Trimester Liver-Specific Biomarkers for Prediction of Intrahepatic Cholestasis in Pregnancy

Erken İkinci Trimester Karaciğer Spesifik Biyobelirteçlerin Gebeliğin İntrahepatik Kolestazındaki Öngörüsü

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ÖZ

Amaç: Gebelikte intrahepatik kolestaz (ICP), gebelikle ilişkili en yaygın karaciğer hastalığıdır ve olumsuz obstetrik sonuçlarla ilişkilidir. ICP'nin tahmini son zamanlarda önemli ilgi görmüştür. Bu çalışmanın amacı, ICP'nin tahmini için ikinci trimesterin başlarında yapılan tarama ve rutin kan parametrelerinin etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya, ICP'li 120 hamile kadın ve kontrol grubunda 120 hamile kadın retrospektif olarak dahil edildi. Erken ikinci trimester karaciğer transaminaz enzimleri (AST: aspartat aminotransferaz, ALT: alanin aminotransferaz), alfa-fetoprotein (AFP) ve AFP-transaminaz oranı değerlendirildi.

Bulgular: Tüm karaciğer spesifik biyobelirteçler (AST, ALT ve AFP) kontrol grubuna kıyasla ICP grubunda anlamlı olarak daha yüksekti. AFP-transaminaz oranı, sağlıklı hamile kadınlara kıyasla ICP grubunda anlamlı olarak daha düşüktü. ICP tahmini için optimal kesme değeri AFP için 31,650 (AUC 0,668, %69,4 duyarlılık, %62,5 özgüllük) ve AFP/transaminaz için 0,048 (AUC 0,755, %53,2 duyarlılık, %90 özgüllük) idi.

Sonuç: İkinci trimesterin başlarında analiz edilen AFP düzeyleri ve AFP-transaminaz oranının analizi, gebeliğin ilerleyen dönemlerinde ICP gelişiminin tahmin edilmesinde yararlı olabilir.

Anahtar Kelimeler: Gebelikte intrahepatik kolestaz, alfa-fetoprotein, AFP-transaminaz oranı, perinatal sonuç

ABSTRACT

Aim: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disease, and it is associated with poor obstetric outcomes. The prediction of ICP has recently attracted significant attention. The objective of this study was to evaluate the efficacy of early second-trimester screening and routine blood parameters in predicting ICP.

Materials and Methods: A total of 120 pregnant women with ICP and 120 pregnant women in the control group were retrospectively included in the study. Early second trimester liver transaminase enzymes (AST: aspartate aminotransferase, ALT: alanine aminotransferase), alpha-fetoprotein (AFP) and the AFP-transaminase ratio were evaluated.

Results: All liver-specific biomarkers (AST, ALT and AFP) were significantly higher in the ICP group compared to the control group. AFP-transaminase ratio was significantly lower in the ICP group compared to healthy pregnant women. The optimal cut off value for ICP prediction was 31.650 (AUC 0.668, 69.4% sensitivity, 62.5% specificity) for AFP and 0.048 (AUC 0.755, 53.2% sensitivity, 90% specificity) for AFP/transaminase.

Conclusion: The analysis of AFP levels and the AFP-transaminase ratio in the early second trimester may be useful in predicting the development of ICP later in pregnancy.

Keywords: Intrahepatic cholestasis of pregnancy, alpha-fetoprotein, AFP-transaminase ratio, perinatal outcome

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) represents the most prevalent pregnancy specific liver disease (1). The global prevalence of this disease is estimated to range from 1 to 27 percent (2). It is a liver disorder that presents with persistent pruritus without a rash, typically developing in the late second and/or third trimester and resolving rapidly after delivery. The primary laboratory finding is an elevated serum bile acid concentration (3). Although the etiology of this condition remains incompletely understood, it is thought to result from a combination of genetic predisposition, hormonal factors, and environmental factors. ICP is associated with a variety of adverse fetal outcomes, including preterm delivery, amniotic fluid with meconium, neonatal respiratory distress, fetal arrhythmia and fetal death (4–6).

Considering all these, early diagnosis is essential for this disease, which causes maternal and fetal morbidity and mortality. There are a limited number of studies on the usability of markers such as PAPP-A (Pregnancy-Associated Plasma Protein A), free β-hCG (beta-human chorionic gonadotropin), and AFP (alpha-fetoprotein) used in first- and second-trimester aneuploidy screening for predicting ICP (7–11). The AFP-transaminase ratio (AFP/ASTxALT) (AST: aspartate aminotransferase, ALT: alanine aminotransferase) is a novel index that has demonstrated efficacy in predicting hepatocellular carcinoma cases, offering better predictive performance than AFP alone and the AFP/WBC (alpha-fetoprotein/white blood cell count) ratio. Given that hepatic deterioration occurs before the manifestation of disease symptoms, the objective of this study was to utilize this index, which has been employed in previous studies, for the early diagnosis of liver disease (12).

In light of the findings from these studies, the objective of this investigation was to evaluate the capacity of AFP and the AFP-transaminase ratio, as determined from early second-trimester screening tests, to predict ICP and their potential to predict perinatal outcomes in pregnant women with ICP.

METHODS

A retrospective study was conducted at the Perinatology Clinic of Ankara Bilkent City Hospital between January 2022 and September 2024. The research protocol was approved by Ankara Bilkent City Hospital Clinical Research Ethics Committee (number: 2-24-353). Data were collected from the hospital's electronic database and patient files.

During the study period, 263 patients presented at the clinic with complaints of pruritus, and 12 patients with elevated liver enzymes.

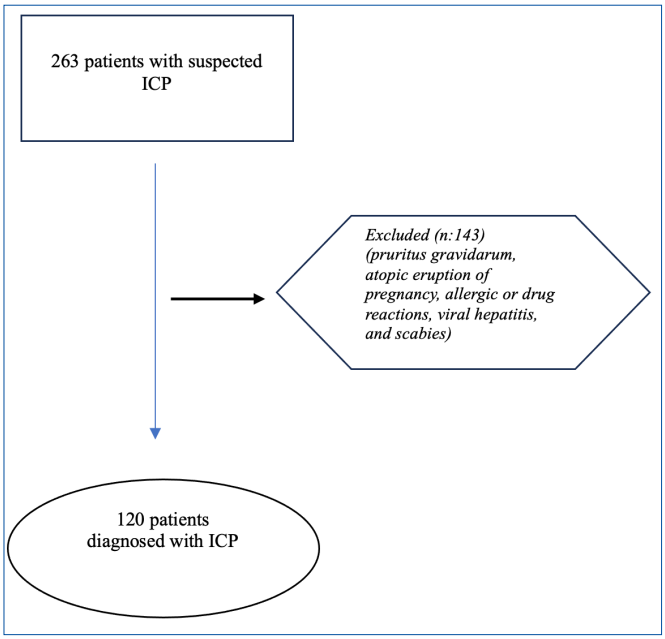

Figure 1. A flow chart of the study

The diagnosis of ICP was confirmed in 111 of the patients who presented with pruritus and in 9 of the patients with elevated liver enzymes. The other patients were diagnosed with conditions such as pruritus gravidarum, atopic eruption of pregnancy, allergic or drug reactions, viral hepatitis, and scabies (figure1). The study population included 240 women, with 120 pregnant women diagnosed with ICP and 120 pregnant women in the control group. In contrast, the control group consisted of the first healthy pregnant women at a similar gestational age examined after each patient included in the case group. Exclusion criteria include maternal comorbidities (e.g., malignancy, cardiovascular or rheumatologic disease, etc.), active viral or bacterial infections, known chronic or acute liver disease, history of bleeding in early pregnancy, history of hyperemesis gravidarum, known or suspected malignancy, multiple gestations, pregnancies obtained by assisted reproductive techniques, or known major fetal anomalies.

Any patient with pruritus without rash in the late second or third trimester should be suspected of having ICP. However, there is no consensus on the diagnosis. In our clinic, patients with both elevated bile acids and typical pruritus in the last trimesters of pregnancy were considered to have ICP according to SFMF (Society for Maternal-Fetal Medicine) recommendations (13). Following the exclusion of other potential etiologies, ICP was diagnosed in cases where symptoms of typical pruritus and total bile acid levels exceeding 10 mmol/L are present. Patients with serum bile acid levels below 40 µmol/L were considered to have mild ICP, and those with levels above 40 µmol/L were considered to have severe ICP (14).

The laboratory data for the all patients included in the study were obtained from gestational ages 15-19 weeks. The AFP-transaminase ratio, which was the focus of the study, was calculated using the formula AFP/ASTxALT (12). A composite adverse perinatal outcome (CAPO) was defined as the occurrence of one or more of the following: APGAR score less than seven at one or five minutes, intrauterine fetal death (IUDF), neonatal intensive care unit (NICU) admission, fetal growth restriction, preterm delivery, preeclampsia, fetal distress, and neonatal death. A comparative analysis was conducted between the ICP and control groups, with a focus on the patients' demographic and obstetric characteristics, as well as the AST, ALT, and AFP values obtained at 15–19 gestational weeks. Additionally, the Receiver Operating Characteristic (ROC) analysis was performed to assess the efficacy of AFP and the AFP-transaminase ratio in predicting CAPO.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, version 22.0) (Armonk, NY: IBM Corp.). Data were tested for normal distribution using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since the data did not have a normal distribution, continuous variables were presented as median and interquartile ranges (IQR). Categorical variables were presented as numbers and percentages. The Mann-Whitney U test was used to compare median values between groups, and the chi-square test was performed to compare categorical variables. A ROC curve analysis was performed to evaluate the performance of AFP and AFP-transaminase indices in predicting the development of ICP. The Youden index was used to determine the highest sensitivity and specificity values. The statistical significance of the results was determined by a p-value less than 0.05.

RESULTS

The study population included 240 women, with 120 pregnant women diagnosed with ICP and 120 pregnant women in the control group. A comparison of the demographic and clinical characteristics, as well as the obstetric features, between the ICP and control groups is presented in Table 1. The ICP group exhibited a statistically significant decrease in gestational age at birth and neonatal weight compared to the control group ($p<0.01$). In the ICP group, there was a statistically significant increase in the cesarean section rate, NICU admission rate, and composite adverse perinatal outcomes compared to the control group ($p<0.01$, $p=0.002$, $p<0.01$, respectively). The most prevalent fetal complication in the CAPO subgroup evaluated in the ICP group was preterm delivery, which occurred in 31.9% of cases. Furthermore, IUFD occurred in one patient in the ICP group (0.8%). No neonatal deaths were observed in either the ICP or control groups.

Table 1. Comparative demographic, clinical characteristics and obstetric features of ICP and control groups

Variable	ICP group (n=120)	Control Group (n=120)	p value
Age (years)	28.6 (7)	29.2 (8)	0.378
Gravidity	2.1 (2)	2.3 (2)	0.088
Parity	0.8 (1)	0.9 (0.9)	0.197
Abortus	0.3 (0)	0.4 (0)	0.630
Gestational age at birth (weeks)	36.9 (1)	38.3 (2)	**<0.001**
Newborn weight (grams)	2967 (613)	3331 (504)	**<0.001**
Cesarean section rate (n, %)	55 (45.8 %)	32 (26.6 %)	**<0.001**
1st minute APGAR <7 (n, %)	10 (8.3 %)	5 (4.2 %)	0.182
5th minute APGAR <7 (n, %)	1 (0.8 %)	0 (0 %)	0.316
NICU admission (n, %)	38 (31.7 %)	18 (15.0 %)	**0.002**
IUFD (n, %)	1 (0.8 %)	0 (0 %)	0.316
CAPO (n, %)	71 (59.1 %)	30 (25 %)	**<0.001**

ICP: intrahepatic cholestasis of pregnancy, NICU: newborn intensive care unit, IUFD: intrauterine fetal death, CAPO: composite adverse perinatal outcome. Results are presented as median (interquartile range). A p-value less than 0.05 is considered statistically significant.

Table 2. Comparison of the early second trimester AST, ALT, AFP values and AFP-transaminase ratio between the ICP and control groups

Variable	ICP group (n=62)	Control Group (n=120)	p value
AFP (IU/ml)	41.3 (20.0)	31.8 (15.1)	**<0.01**
AST (U/L)	35.5 (17)	16.4 (8)	**<0.01**
ALT (U/L)	48.3 (37)	15.1 (6)	**<0.01**
AFP-Transaminase ratio	0.086 (0.10)	0.182 (0.16)	**<0.01**

ICP: intrahepatic cholestasis of pregnancy, AFP: alpha fetoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AFP-transaminase ratio: AFP / AST x ALT. Results are presented as median (interquartile range). A p-value less than 0.05 is considered statistically significant.

Table 3. Early second trimester AST, ALT, AFP values and AFP-transaminase ratio in patients with mild and severe ICP

Variable	Mild ICP (n=45)	Severe ICP (n=17)	p value
AFP (IU/ml)	41.0 (18.8)	42.5 (28.3)	0.469
AST (U/L)	28.9 (16)	58.0 (58)	0.354
ALT (U/L)	40.4 (34)	75.3 (97)	0.232
AFP-Transaminase ratio	0.0921 (0.11)	0.685 (0.11)	0.232

Patients with maximum serum bile acid level below 40 µmol/L were grouped as mild ICP, patients with maximum serum bile acid level above 40 µmol//L were grouped as severe ICP. ICP: intrahepatic cholestasis of pregnancy. AFP: alpha fetoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AFP-transaminase ratio: AFP / AST x ALT. Results are presented as median (interquartile range). A p-value less than 0.05 is considered statistically significant."

Table 4. The ROC curve analysis for the performance of early second trimester AFP value and AFP-Transaminase ratio for prediction of ICP

Variable	AUC	95%Confidence Interval	Cut-off value	Sensitivity	Specificity	J value	p value
AFP-Transaminase ratio	0.755	0.676-0.835	0.048	53.2%	90%	0.432	**<0.001**
AFP (IU/ml)	0.668	0.582-0.753	31.650	69.4%	62.5%	0.319	**<0.001**

AUC: area under the curve, AFP/transaminase ratio: AFP / AST x ALT, AFP: alpha fetoprotein, J value: The Youden Index.

The mean diagnosis week for 120 pregnant women with ICP was 32.6 weeks, ranging from 21 to 39 weeks. Early second-trimester AFP, AST, and ALT values were available for 62 of the pregnant women included in the study with a diagnosis of ICP. Data for early second-trimester values were obtained at the earliest 15th and latest 19th gestational week, with a mean gestational age of 17.2 weeks. Statistical analysis was performed for AFP, AST, ALT, and the AFP-transaminase ratio based on the results from 62 pregnant women. The AFP, AST, and ALT levels were found to be significantly elevated in the ICP group ($p<0.01$). The AFP-transaminase ratio was shown to be considerably lower in the ICP group compared to the control group ($p<0.01$). The results of the comparison of early second-trimester biomarkers of pregnant women are presented in Table 2.

No statistically significant difference was observed between the mild and severe ICP groups concerning second-trimester AFP, AST, ALT, and AFP-transaminase ratio. Table 3 illustrates the comparative outcomes of second-trimester biomarkers between mild and severe ICP cases. ROC curve analysis demonstrated that the AFP-transaminase ratio and AFP may serve as valuable predictors of the subsequent development of ICP in pregnancy. The AFP-transaminase ratio showed a higher area under the curve (AUC) in comparison to the AFP marker (AUC 0.755, 95%CI: 0.676-0.835, $p<0.01$; AUC 0.668, 95% CI: 0.582-0.753, $p<0.01$, respectively). Optimal cut-off values for the AFP-transaminase ratio and AFP in predicting ICP development were 0.048 (53.2% sensitivity and 90% specificity) and 31.650 (69.4% sensitivity and 62.5% specificity), respectively. Table 4 presents the results of the ROC curve analyses. Furthermore, ROC analysis was performed for AFP-transaminase and AFP values in CAPO prediction, yielding an AUC of 0.551 (95% CI: 0.461-0.641, $p = 0.245$) and an AUC of 0.621 (95% CI: 0.537-0.706, $p = 0.005$), respectively.

DISCUSSION

The primary findings of the present study indicate that early second-trimester AFP levels and AFP-transaminase ratio have the potential to serve as predictors of ICP. Specifically, it has been demonstrated that the markers that are within the normal range for ICP disease diagnosed in late pregnancy can serve as a predictor of ICP in early pregnancy. However, the clinical significance of these values in predicting mild and severe ICP remains to be fully elucidated. In addition, early second-trimester AFP, AST, and ALT levels may serve as additional risk factors for the development of ICP.

ICP is a prevalent liver disease that occurs during pregnancy. It remains a significant cause of fetal morbidity and mortality (5,13). The etiology of ICP remains elusive, with the underlying mechanisms still not fully understood. However, it is well established that maternal bile acids easily cross the placental barrier. In healthy pregnancies, the placental gradient effectively eliminates bile acids from the fetal compartment, whereas this function is impaired in pregnancies complicated by ICP (15). High concentrations of bile acids in amniotic fluid, fetal blood and fetal tissues are thought to

be associated with fetal morbidity and mortality. Bile acids are also considered to cause preterm labor by increasing the expression of myometrial oxytocin receptors (16,17). Pregnancies with ICP are at increased risk for spontaneous or iatrogenic preterm delivery, meconium-stained amniotic fluid, neonatal respiratory distress syndrome, NICU admission, fetal growth restriction, and IUFD (3,4,13,15). In the present study, the rates of cesarean section, NICU admission, and cumulative CAPO incidence were significantly higher in the ICP group. The most prevalent adverse perinatal outcome was preterm delivery. Furthermore, the ICP group demonstrated lower neonatal birth weight and birth week. Notably, IUFD occurred in one patient who was followed up with ICP. The patient was in the mild ICP group, and fetal death occurred at 35 weeks of gestation. Studies and meta-analyses have shown that the risk of fetal death is correlated with elevated bile acid concentrations and that the risk is elevated significantly when the bile acid levels exceed 100 µmol/L (13,17). No IUFD occurred in patients in the severe ICP group in the study. A potential explanation for this observation may be the relatively limited number of patients with bile acid levels exceeding 100 µmol/L. Consistent with the current literature, cases in the ICP group in the present study exhibited a higher prevalence of pregnancy complications and adverse perinatal outcomes.

ICP typically develops during the late second and third trimesters of pregnancy (18,19). In this context, parameters associated with first- and second-trimester screening tests may help predict this disease, which typically occurs in late pregnancy. A correlation has been established between reduced serum PAPP-A levels and the onset of ICP (7,8). Despite research indicating elevated free β-hCG levels in patients with ICP, no statistically significant difference has been found (8,9,11). Furthermore, studies comparing the levels of AST and ALT in the first and second trimesters have demonstrated that these values are elevated in pregnant women with ICP (9,20). The study revealed that AST and ALT levels measured exhibited a statistically significant increase in the ICP group when compared to the control group. The findings of this study are consistent with the existing literature on the subject. This study demonstrates that in cases of ICP, despite normal liver transaminase levels in early pregnancy, they may be elevated compared to those observed in healthy pregnancies. Based on this finding, the potential of these parameters in predicting disease may be the subject of further research.

AFP, which is specific for the liver, has also been studied for this condition, which is one of the most essential liver diseases of pregnancy, the etiology of which is still unclear and which causes liver disorders and diseases after pregnancy. In studies comparing AFP and free β-hCG levels in mid-trimester screening tests, no statistically significant difference was found between pregnancies with ICP and those with healthy pregnancies (9–11). In the present study, AFP values were found to be significantly higher than those in the control group. In comparison to the other studies mentioned, the present study included a higher number of pregnant women with ICP. Furthermore, AFP serves as a marker that can reflect the degree of hepatocyte damage (21,22). The elevated AFP levels observed in the early stages of pregnancy complicated by ICP, as compared to the control group, lend support to our current hypothesis. AFP is also the most commonly used tumor marker in the screening and diagnosis of hepatocellular carcinoma (23). In addition to hepatic malignancy, an increase in serum AFP levels can also be observed in regeneration after liver cell necrosis and non-cancerous liver diseases including viral hepatitis, liver fibrosis. Many studies have shown that AFP increases and decreases in parallel with AST and ALT values synthesized by the liver, thus AFP may indirectly reflect the level of liver inflammation and damage (24). A study published in 2019 demonstrated that the AFP-transaminase ratio (AFP/(ASTxALT)) is a highly sensitive and specific predictor of hepatocellular carcinoma, outperforming all other investigated parameters. It has also been reported that the AFP-transaminase ratio can be used to estimate therapeutic effect and evaluate prognosis (12). In light of the results of this study, we evaluated the potential of the AFP-transaminase ratio as a predictor of ICP. In the present study, AFP levels were found to be significantly elevated, while the AFP-transaminase ratio was significantly lower. When ROC analysis was performed on both parameters, it was revealed that both parameters exhibited the potential to predict the development of ICP. According to these results, the AFP-transaminase ratio showed better performance in predicting the development of ICP compared to AFP. Additionally, the present study found this ratio to demonstrate a high degree of specificity.

One of the strengths of this study is the utilization of biomarkers commonly employed in routine early second-trimester screening for ICP prediction, obviating the need for additional parameters. Another strength of this study is that the markers were examined not only for their prediction of ICP but also for their potential association with adverse obstetric outcomes. The study's limitations include its retrospective design and the fact that it was conducted at a single center with a relatively small patient population. Additionally, the absence of early second-trimester biomarker data for all ICP cases may impede the interpretation of the results.

CONCLUSION

ICP is a significant obstetric complication with the potential to result in adverse perinatal outcomes. Therefore, predicting this condition may be beneficial in order to perform diagnostic tests at an earlier

stage of pregnancy and to initiate the necessary antenatal follow-up and treatment on time. The present study demonstrated that liver transaminases and AFP, as well as the AFP-transaminase ratio, may be useful in predicting ICP. Further insight may be gained through the implementation of randomized studies with a larger patient cohort.

Ethics Committee Approval: The research protocol was approved by Ankara Bilkent City Hospital Clinical Research Ethics Committee (number: 2-24-353).

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Behçet's Disease and Pregnancy: A Retrospective Cross-Sectional Study on the Risk of Preterm Birth and the Role of Mucocutaneous Activity

Behçet Hastalığı ve Gebelik: Erken Doğum Riski ve Mukokütanöz Aktivitenin Rolü Üzerine Retrospektif Kesitsel Bir Çalışma

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ÖZ

Amaç: Bu çalışma, Behçet hastalığı (BH) olan kadınlarda tanı öncesi ve sonrası gebelik sonuçlarını değerlendirmeyi ve karşılaştırmayı amaçladı.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışmaya BH tanısı alan 30 kadının 100 gebeliği dahil edildi. Klinik özellikler, tedaviler ve obstetrik sonuçlar incelendi. Gebelik sonuçları, BH tanısı öncesinde ve sonrasında gerçekleşen gebelikler arasında karşılaştırıldı. Ayrıca, olumsuz sonuçlar olmadan canlı doğumla ilişkili faktörler analiz edildi.

Bulgular: 100 gebeliğin 52'si tanı öncesinde, 48'i tanı sonrasında gerçekleşmişti. Tanı sonrası grupta doğum haftası anlamlı olarak daha düşük bulundu ($p < 0.001$), preterm doğum oranı daha yüksekti (%25,7 ve %7,3; $p = 0.03$) ve sezaryen doğum oranları artmıştı (%54,3 ve %19,5; $p = 0.002$). Düşük, yenidoğan yoğun bakım yatışı, yenidoğan sarılığı, anomali veya perinatal mortalite açısından anlamlı fark saptanmadı. Çok değişkenli analizde eritema nodozum olumsuz gebelik sonuçlarının tek bağımsız prediktörü olarak bulundu (OR 5,66; %95 GA: 1,07–29,92; $p = 0.041$).

Sonuç: BH tanısı sonrasında gerçekleşen gebelikler, önceki gebeliklere göre preterm doğum ve sezaryen doğum açısından artmış risk ile ilişkilidir. Eritema nodozum varlığı, olumsuz obstetrik sonuçlarla bağımsız olarak ilişkili bulunmuştur.

Anahtar Kelimeler: Behçet, Gebelik, Preterm, Sezaryen, Kolşisin

ABSTRACT

Aim: This study aimed to evaluate and compare the pregnancy outcomes of women with Behçet's disease (BD) before and after the diagnosis.

Materials and Methods: This retrospective cross-sectional study included 100 pregnancies from 30 women diagnosed with BD. Clinical characteristics, treatments, and obstetric outcomes were assessed. Pregnancy outcomes were compared between those occurring before and after BD diagnosis. Additionally, factors associated with live birth without adverse outcomes were analyzed.

Results: Of the 100 pregnancies, 52 occurred before and 48 after the diagnosis of BD. The post-diagnosis group had markedly lower gestational age at delivery ($p < 0.001$), a higher rate of preterm birth (25.7% vs. 7.3%, $p = 0.03$), and increased cesarean delivery rates (54.3% vs. 19.5%, $p = 0.002$). No significant differences were observed in miscarriage, NICU admission, neonatal jaundice, anomaly, or perinatal mortality. In multivariate analysis, erythema nodosum was the only independent predictor of adverse pregnancy outcomes (OR 5.66, 95% CI: 1.07–29.92, $p = 0.041$).

Conclusion: Pregnancies following the diagnosis of BD are associated with increased risks of preterm birth and cesarean delivery. Patients with erythema nodosum was independently associated with adverse obstetric outcomes. Close monitoring remains essential to optimize maternal and fetal health in patients with BD.

Keywords: Behcet, Pregnancy, Preterm, Cesarean, Colchicine

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INTRODUCTION

Behçet's diseases (BD) is a multisystemic vasculitis characterized by systemic manifestations that may impact the gastrointestinal tract, neurological system, vascular systems, and joints, in addition to recurring oral and vaginal ulcers, ocular involvement, and cutaneous lesions. In current medicine, it gained authority in 1937 after described by Hulusi Behçet (1,2). BD is characterized by its ability to impact small, medium, and large diameter arteries in both arterial and venous systems, differentiating it from other vasculitis.

Türkiye has the highest incidence (80–370 cases per 100,000), followed by Japan, Korea, China, Iran, Iraq, and Saudi Arabia (3). The condition is more frequent among migrants from high-risk locations in low-prevalence nations like Europe and America. It mostly affects adults aged 20 to 40, particularly males (4). The main clinical manifestation is painful, recurrent mucocutaneous ulcers. Ocular involvement (two-thirds of patients), vascular complications (one-third), and central nervous system involvement (10–20%) result in the greatest morbidity and mortality. Cutaneous and articular symptoms are prevalent in BD, although renal and peripheral nervous system involvement is rare (5).

Although disease activity decreases in many cases among women with BD during pregnancy, an increase in the risk of pregnancy complications has been reported (6). In different studies, it has been found that complications such as miscarriage, preterm birth, cesarean section, intrauterine fetal death, HELLP syndrome, and immune thrombocytopenia are more frequently observed in patients with BD compared to healthy pregnancies (6,7). Additionally, in pregnant women with active disease who are using colchicine, adverse obstetric outcomes such as preterm birth and low birth weight are more frequently observed. These findings indicate that pregnant women with BD should be closely monitored throughout their pregnancy (8).

This study aimed to evaluate and compare pregnancy outcomes before and after the diagnosis of Behçet's disease and to explore the impact of disease activity and treatment regimens during pregnancy and the postpartum period.

MATERIAL AND METHODS

Study Population

This cross-sectional and retrospective analysis included 30 patients diagnosed with BD and examined 100 pregnancy outcomes from January 2025 to June 2025, selected from patients in the outpatient clinic throughout this period. This research thoroughly assessed the outcomes of 100 pregnancies in individuals diagnosed with BD, studying the pregnancy results in detail both before as well as after the diagnosis. Detailed information about the pregnancies of each patient diagnosed with BD, were acquired cross-sectionally via both hospital records and individual conversations with the patients. A certain diagnosis of BD was determined according to the International Study Group (ISG) criteria (1990), resulting in recurrent oral aphthous ulcers alongside at least two of the following minor criteria: recurrent genital ulcers, skin lesions, ocular involvement, or a positive pathergy test (9). The exclusion criteria were limited clinical data, a conflicting diagnosis of BD or absence of standard diagnostic criteria, and the presence of concurrent rheumatologic conditions. The research received approval from the ethical committee of Ümraniye Training and Research Hospital (Date and number: 16.01.2025/474) and was conducted in accordance with the Declaration of Helsinki. Data collection and reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.

Maternal - neonatal Parameters and Obstetric Outcomes

The demographic and clinical features of all patients were examined, including age, education, body mass index (BMI), age at symptom onset, and age at diagnosis. Clinical symptoms of BD including oral aphthae, vaginal ulcers, erythema nodosum, papulopustular eruptions, and involvement of the ophthalmic, musculoskeletal, vascular, central nervous system (CNS), and gastrointestinal system (GIS), were reported. Furthermore, treatments including low dose aspirin and colchicine, the analysis included obstetric parameters such as gestational age at delivery, mode of delivery, neonatal birth weight, NICU admission, neonatal jaundice, presence of fetal anomalies, and perinatal mortality (including miscarriage, elective termination, and stillbirth). Additionally, maternal outcomes such as preterm birth, hypertensive disorders of pregnancy (including preeclampsia and gestational hypertension), gestational diabetes mellitus, fetal growth restriction, and live birth rates were assessed. Adverse outcomes were characterized as miscarriage, stillbirth, fetal abnormality, and HELLP syndrome. The assessment of disease activity during pregnancy and the postpartum period was carried out. Additionally, comorbid conditions and results of the pathergy test were recorded. We assessed disease activity during pregnancy. Patients presenting no disease activity and symptoms linked to BD were considered to be in remission. A flare-up was considered to be present if symptoms escalated or emerged during gestation. The administration of any medicine for the treatment of BD during pregnancy was also documented. Pregnancy outcomes before and after the diagnosis of BD were compared, and factors associated with live births without adverse outcomes in pregnancies occurring after the diagnosis were evaluated.

Preterm delivery was characterized as a birth occurring before to 37 weeks of gestation. Gestational hypertension is characterized by new-onset systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg occurring after 20 weeks of gestation, without the presence of proteinuria or clues of end-organ failure. Preeclampsia is characterized by gestational hypertension with proteinuria (≥300 mg/24 h or a protein/creatinine ratio ≥0.3) or, in the absence of proteinuria, by manifestations of maternal organ malfunction, as per ACOG criteria (9).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v22.00). Armonk, IBM Corp). Descriptive data were expressed as mean, median, standard deviation, and minimum-maximum. The normality of the distribution of the variables was evaluated using the Kolmogorov–Smirnov test. Chi-square tests (Fisher's exact test if expected counts were below five) were used for categorical data. The Mann–Whitney U test was used to compare the two groups. In statistical analyses, a significance level of $p<0.05$ was considered.

RESULTS

A total of 100 pregnancy outcomes from 30 patients diagnosed with BD were included in the study. The mean age of the patients was 45.5 years (SD: 9.6), and the mean age at diagnosis was 30.8 years (SD: 8.8). All patients were married and 25 (83.3%) were housewives, 2 (6.7%) were workers, and 3 (10%) were retired. While 24 patients were non-smokers, 4 were current smokers, and 2 were former smokers. None of the patients smoked during pregnancy. Demographic and clinical characteristics of patients with BD are presented in Table 1.

Comorbidities were present in 40% of the patients, including hypertension (n = 4), diabetes mellitus (n = 3), arrhythmia (n = 2), coronary artery disease (n = 2), and chronic obstructive pulmonary disease (n = 1).

The most common clinical manifestation was oral ulcers, observed in all patients (100%), followed by genital ulcers in 25 (83.3%), musculoskeletal involvement in 13 (43.3%), erythema nodosum in 9 (30%), papulopustular lesions in 7 (23.3%), and ocular involvement in 5 (16.7%). Pathergy positivity was present in 16 (53.3%) patients. Vascular involvement was observed in 3 patients (10%), while central nervous system and gastrointestinal involvement were not reported.

None of the patients had infertility, and all pregnancies were spontaneous. The mean number of gravidas was 5 (SD: 2.7; range: 1–9), the mean parity was 2.7 (SD: 0.9; range: 1–5), and the mean number of abortions was 2.2 (SD: 2.2; range: 0–6).

Table 1. Demographic and Clinical Characteristics of Patients with Behçet's Disease

Age, years	45.5 (9.6)
Educational level	
Illiterate	3 (10%)
Primary school	13 (43.3%)
Middle school	6 (20%)
High school	5 (16.7%)
University	3 (10%)
Body mass index, kg/m²	26.9 (4.3)
Age at symptom onset, years	24.5 (8.2) (10-45)
Age at diagnosis, years	30.8 (8.8) (21-56)
Clinical manifestations	
Oral aphthae	30 (100%)
Genital ulcers	25 (83.3%)
Erythema nodosum	9 (30%)
Papulopustular lesion	7 (23.3%)
Ocular involvement	5 (16.7%)
Musculoskeletal involvement	13 (43.3%)
Pathergy positivity	16 (53.3%)
Vascular involvement	3 (10%)
CNS involvement	-
GIS involvement	-
Comorbidity, yes	12 (40%)

Data are presented as mean (SD) or n (%) or (min-max)
CNS Central Nervous System, GIS Gastrointestinal System

Comparison of Pregnancy Outcomes Before and After the Diagnosis of Behçet's Disease

Of the pregnancies, 52 (52%) occurred before the diagnosis of BD, while 48 (48%) occurred after the diagnosis. Gestational age at birth was markedly lower in the post-diagnosis group ($p<0.001$), and the rate of preterm birth was higher in this group ($p = 0.03$). Cesarean delivery was more frequent in the post-diagnosis group ($p = 0.002$). The use of anticoagulant treatment was also significantly higher in the post-diagnosis group ($p = 0.02$). Other variables, including birth weight, miscarriage, NICU admission, neonatal jaundice, anomaly, and mortality, did not differ significantly between the groups ($p>0.05$) (Table 2).

Preterm birth was observed in a total of 12 (12%) pregnancies. The underlying causes included COVID-19 infection in 2 patients, HELLP syndrome in 1 patient, preeclampsia in 1 patient, oligohydramnios in 1 patient, polyhydramnios in 1 patient, pulmonary thromboembolism during pregnancy in 1 patient, and spontaneous preterm labor in 4 patients.

Final pregnancy outcomes were assessed in relation to BD diagnosis. The rate of live births was 78.8% before diagnosis and 70.8% after diagnosis ($p = 0.64$). Miscarriage occurred in 19.2%

Table 2. Maternal and Fetal Outcomes Before and After Behçet's Disease Diagnosis

	Pregnancies before diagnosis n=52	Pregnancies after diagnosis n=48	p
Mothers age at birth, years	23.7 (5.5)	30.1 (5.2)	<0.001
Gestational age at birth, weeks	39.1 (1.74)	37.4 (2.57)	<0.001
Birth weight, gram	3183.4 (542.2)	3245.4 (585.4)	0.631
Mode of delivery			
Vaginal delivery	33 (80.5%)	16 (45.7%)	0.002
Cesarean delivery	8 (19.5%)	19 (54.3%)	
Preterm birth	3 (7.3%)	9 (25.7%)	0.03
Premature rupture of membranes	-	3 (8.6%)	0.09
Fetal growth restriction	3 (7.3%)	1 (2.9%)	0.62
Miscarriage	10 (19.2%)	12 (25%)	0.64
GA at miscarriage	8.2 (1.6)	8.1 (1.6)	1
Gestational Diabetes Mellitus	-	1 (2.9%)	0.46
Gestational Hypertension	-	3 (8.6%)	0.09
Preeclampsia	2 (4.9%)	3 (8.6%)	0.65
Treatments			
Low-dose aspirin	1 (2.4%)	5 (14.3%)	0.08
Anticoagulant	1 (2.4%)	7 (19.4%)	0.02
NICU	4 (9.8%)	2 (5.9%)	0.68
Neonatal jaundice	10 (24.4%)	8 (23.5%)	0.57
Anomaly	1 (2.4%)	-	0.54
Mortality	11 (21.2%)	14 (29.1%)	0.26

Data are presented as mean (SD) or n (%)

of pregnancies before diagnosis and in 25% after. The mean gestational week at miscarriage was 8.2 (SD: 1.6; range: 6–12) in pregnancies before the diagnosis of BD and 8.1 (SD: 1.6; range: 5–10) in those occurring after the diagnosis. Termination rates were similar in both groups (1.9% vs. 2.1%), and stillbirth was reported only one patient in the post-diagnosis group (2.1%). No statistically significant differences were observed between the groups (Table 3).

A stillbirth was observed in one patient, a 38-year-old woman in her fourth pregnancy, which occurred after the diagnosis of BD. The stillbirth occurred at 28 weeks of gestation due to preeclampsia, with a fetal weight of 1600 grams. The patient had been receiving colchicine treatment prior to pregnancy but discontinued it during gestation.

Of the two pregnancy terminations, one was performed before and the other after the diagnosis of BD. Both were elective procedures initiated at the patient's request.

Among the 12 patients who had miscarriages after the diagnosis of BD, 9 (75%) were using colchicine during pregnancy, while 3 (25%) were not. There was no significant difference in miscarriage rate between colchicine users and non-users (p = 0.74).

Factors Associated with Live Birth and Fetal Well-being in Pregnancies Affected by Behçet's Disease

Among pregnancies after BD diagnosis (n=48), erythema nodosum (p = 0.02) and ocular involvement (p=0.04) were significantly more common in those without a healthy live birth. Other variables, including age at symptom onset, age at diagnosis, maternal age at delivery, genital ulcers, papulopustular lesions, musculoskeletal involvement, pathergy positivity, vascular involvement, colchicine use during pregnancy, and preconception disease activity, were not significantly different between the groups (p>0.05 for all) (Table 4).

In the multivariate logistic regression analysis, variables that were significant in the univariate analysis, including the presence of erythema nodosum and ocular involvement, were included along

Table 3. Final Pregnancy Outcomes Before and After Behçet's Diagnosis

	Pregnancies before diagnosis	Pregnancies after diagnosis	p
Live birth	41 (78.8%)	34 (70.8%)	0.64
Miscarriage	10 (19.2%)	12 (25%)	
Termination	1 (1.9%)	1 (2.1%)	
Stillbirth	-	1 (2.1%)	

Data are presented as n (%)

Table 4. Factors Associated with Live Births Without Adverse Outcomes in Pregnancies Following the Diagnosis of Behçet's Disease (n=48)

	Live birth without adverse outcomes		p
	Yes (n=34)	No (n=14)	
Age at symptom onset, years	22.9 (4.6)	22.2 (4.2)	0.332
Age at diagnosis, years	26.1 (5.1)	24.2 (5.9)	0.06
Mother's age at birth	29.8 (5.1)	30.5 (5.5)	0.724
Symptoms in patients			
Oral aphthae	34 (100%)	14 (100%)	1
Genital ulcers	29 (85.3%)	10 (71.4%)	0.41
Erythema nodosum	14 (41.2%)	11 (78.6%)	**0.02**
Papulopustular lesion	8 (23.5%)	6 (42.9%)	0.29
Ocular involvement	5 (14.7%)	6 (42.9%)	**0.04**
Musculoskeletal involvement	16 (47.1%)	10 (71.4%)	0.21
Pathergy positivity	15 (44.1%)	6 (42.9%)	0.59
Vascular involvement	4 (11.8%)	-	0.31
Colchicine during pregnancy	21 (61.8%)	9 (64.3%)	0.56
Low-dose aspirin during pregnancy	5 (14.7%)	-	0.85
Anticoagulant during pregnancy	6 (17.6%)	1 (50%)	0.35
Active disease activity before pregnancy	10 (29.4%)	2 (40%)	0.63
Active disease activity during pregnancy	18 (52.9%)	1 (20%)	0.34

Data are presented as mean (SD) or n (%)

Table 5. A Multivariate Logistic Regression Analysis of Adverse Pregnancy Outcomes in Behçet's Disease

	B	S.E.	Exp (B)	95% CI		p
				Lower	Upper	
Maternal age	-0.047	0.76	0.954	0.822	1.107	0.533
Erythema nodosum	1.734	0.850	5.66	1.071	29.92	**0.041**
Ocular involvement	1.338	0.834	3.81	0.743	19.551	0.109
Colchicine during pregnancy	-1.01	0.863	0.362	0.067	1.967	0.239

with maternal age and colchicine use, considering their potential impact on pregnancy outcomes. The presence of erythema nodosum was identified as an independent risk factor for adverse pregnancy outcomes, with an odds ratio of 5.66 (95% CI: 1.07–29.92, p=0.041). Other variables, including maternal age, colchicine use during pregnancy, and ocular involvement, were not statistically significant (Table 5).

Disease Characteristics and Management of Behçet's Disease in Pregnancy

Of the 48 pregnancies that occurred after the diagnosis of BD, colchicine was used in 30 (62.5%) pregnancies, azathioprine was used in 2 (4.2%), and sulfasalazine was used in 1 (2.1%) during the gestational period. As a result of 30 pregnancies using colchicine, 21 resulted in live births, 8 in abortions, and 1 was terminated at the patient's request.

Among the pregnancies that occurred after the diagnosis of BD, the disease was active in 12 pregnancies (25%) and in remission in 27 (56.3%) at the time of conception. Disease activation occurred in 19 (39.5%) pregnancies, while the disease remained stable or in remission in the other pregnancies. Of the 19 pregnancies with flare-ups, 11 had active disease prior to conception. Flare-ups occurred in the first trimester in 12 pregnancies, in the second trimester in 12, and in the third trimester in 7.

The most common manifestations during flares included oral aphthae alone in 5 pregnancies, oral aphthae and genital ulcers in 5, oral aphthae, genital ulcers, and erythema nodosum in 1, oral aphthae and erythema nodosum in 2, genital ulcers alone in 2, uveitis in 1, arthritis in 2, and arthritis with thrombosis in 1 pregnancy.

In three patients, BD was first diagnosed during pregnancy following presentations of pulmonary thromboembolism, deep vein thrombosis, and genital ulcers, respectively.

Treatment was escalated due to disease activation in 10 (20.8%) pregnancies, reduced in 10 (20.8%) pregnancies, and remained unchanged in 28 (58.3%) pregnancies. Following delivery, an increase in disease activity was observed in 14 pregnancies (29.2%), while the disease remained stable in the others.

DISCUSSION

This study evaluated pregnancy related obstetric outcomes and disease related factors in patients with BD, both before and after the diagnosis. Our findings indicate that pregnancies occurring after the diagnosis of BD have higher rates of preterm birth and cesarean delivery. The presence of erythema nodosum was an independent predictor of adverse pregnancy outcomes.

In this study, 12% of all pregnancies resulted in preterm birth, and among pregnancies following the diagnosis of BD this rate was significantly higher compared to those that occurred before the diagnosis (25.7% vs. 7.3%). This highlights the impact of disease activity or treatment timing on obstetric outcomes. In a population-based study using California birth registry data, Horomanski et al. similarly reported that 25% of pregnancies in women with systemic vasculitis, including those with BD, resulted in preterm birth. Importantly, the adjusted relative risk for preterm birth in patients with vasculitis was found to be 3.21 (95% CI: 2.15–4.79), indicating more than a threefold increased risk compared to the general population (10). In the same study by Horomanski et al., hypertensive disorders in pregnancy were also found to be significantly increased among women with vasculitis (10). In our study, hypertensive complications did not differ significantly before and after BD diagnosis. Preeclampsia was observed in 4.9% of pregnancies before diagnosis and 8.6% of pregnancies after diagnosis, while gestational hypertension was only observed in the post-diagnosis group (8.6%). Despite this numerical increase, the differences were not found to be statistically significant. The slightly higher rates in the post-diagnosis group can be attributed to the older maternal age observed in these pregnancies, rather than the direct effect of BD (10).

In a large population-based registry study, Chan et al. reported an increased risk of gestational diabetes in women with BD (adjusted OR: 1.89, 95% CI: 1.10–3.25), whereas fetal outcomes were not adversely affected (11). Similarly, in our cohort, we did not observe a statistically significant difference in neonatal complications, congenital anomalies, or NICU admissions between pregnancies occurring before and after the diagnosis of diabetes. Specifically, although gestational diabetes was more frequently observed after diagnosis in our series, the difference did not reach a statistically significant level, likely due to the smaller sample size.

In our study, the cesarean section rate in pregnancies occurring after the diagnosis of BD was significantly higher compared to pregnancies before the diagnosis (54.3% vs. 19.5%, $p = 0.002$). This finding is consistent with previous reports suggesting that patients with BD may have an increased risk of cesarean delivery. As suggested in the literature, a possible explanation is that doctors may prefer cesarean delivery in patients with a history of genital ulcers due to concerns about triggering an inflammatory response in the genital area. Vaginal birth, especially if associated with trauma, could theoretically worsen local disease activity (12,13).

In our study, apart from early birth and delivery method, no significant relationship was found between BD and other adverse obstetric outcomes such as miscarriage, fetal growth restriction, admission to the NICU, or perinatal mortality. When examining factors associated with live birth without adverse outcomes, univariate analysis revealed that conditions such as erythema nodosum and ocular involvement were significantly associated with poor outcomes. However, in the multivariable logistic regression, only erythema nodosum remained an independent determinant. Disease activity before and during pregnancy showed no statistically significant association with obstetric outcomes. Previous studies have identified ocular involvement and a history of thrombotic events in BD as risk factors for adverse pregnancy outcomes. In some cohorts, the increased risk of miscarriage has been attributed to placental thrombotic events, suggesting a possible role of subclinical vasculitis or a procoagulant tendency in the pathogenesis of pregnancy loss (12,13).

In our study, disease flare-ups were observed in approximately 40% of pregnancies that occurred after the diagnosis of BD, with the most common symptoms being oral aphthae and genital ulcers. In the literature, there are varying results regarding the effect of pregnancy on the activity of BD. In a combined analysis of 21 case reports involving 25 patients and 31 pregnancies, disease flares were reported in 51.6%, remission in 45%, and unchanged cases in 3.2%, indicating that pregnancy may have variable effects on disease activity. Similarly, a review summarizing data from an 11-case series involving 339 patients showed that 52% experienced disease improvement during pregnancy, while 27% experienced flare-ups (12). These findings support the notion that pregnancy can have variable effects on BD, ranging from improvement to worsening or no change. In our cohort, disease exacerbations were observed across all trimesters, with the highest frequency in the first and second trimesters, followed by the third trimester. Regarding the timing of exacerbations, findings in the literature remain inconsistent. In the study by Hamza et al., most flares occurred during the third trimester, whereas Bang et al. reported most exacerbations during the first trimester (14,15).

In line with our results, the most common symptoms during pregnancy flares were oral ulcers and genital ulcers, and previous studies have also reported oral ulcers, genital ulcers, and erythema nodosum as predominant features during pregnancy. In our cohort,

thrombotic complications were observed in only one patient, and ocular flare-ups were not reported. Similarly, in the literature, more severe manifestations such as ocular involvement, Budd–Chiari syndrome, or cerebral venous sinus thrombosis have been rarely described during pregnancy (16,17). These observations indicate that the worsening of the disease during pregnancy is not common, but is generally limited to mucocutaneous activity and rarely affects major organ systems.

In BD, colchicine is one of the first-line treatments, especially for mucocutaneous involvement, and is considered safe during both pregnancy and breastfeeding. In patients with refractory mucocutaneous findings or vascular or ocular involvement, azathioprine is commonly used and is considered safe during pregnancy and breastfeeding, like colchicine (18, 19). In our cohort, 62.5% of the patients were treated with colchicine, 4.2% with azathioprine, and one patient was treated with sulfasalazine due to resistant joint involvement. Eight of the 30 pregnancies exposed to colchicine ended in miscarriage; however, no fetal anomalies were observed in any of the cases exposed to colchicine. Furthermore, in our study, colchicine use was not significantly associated with miscarriage or with adverse outcomes, supporting its continued use during gestation in appropriate clinical settings.

Although our findings are broadly consistent with previous studies, some differences were observed that may be explained by variations in study design, patient selection, and treatment approaches across cohorts. Unlike multicenter prospective studies with larger and more diverse populations, our study was conducted in a single tertiary center with a relatively limited sample size, which may have influenced the generalizability of the results. In addition, the retrospective design and the relatively homogeneous treatment regimens within our cohort might have contributed to discrepancies with earlier reports. These factors, together with the inherent challenges of assessing disease activity and treatment impact during pregnancy, should be considered when interpreting our results.

In conclusion, we showed that pregnancies occurring after the diagnosis of BD were associated with an increased risk of preterm birth and cesarean delivery; however, other obstetric complications such as miscarriage, fetal growth restriction, and neonatal morbidity did not significantly increase. Especially, erythema nodosum was an independent predictor of adverse pregnancy outcomes. Colchicine, widely used in BD, appeared to be safe during pregnancy and was not associated with adverse fetal outcomes. These results underscore the importance of individualized risk assessment and close obstetric and rheumatologic monitoring for pregnant women with BD.

Ethical approval: Ethical approval was obtained from the ethical committee of Ümraniye Training and Research Hospital (Date and number: 16.01.2025/474) Consent for study participation was obtained from all patients or their guardians.

Conflict of interest: The authors declare that there is no conflict of interest.

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Maternal Neutrophil gelatinase assosiated lipocalin level in last trimester isolated intrauterine growth-restriction

Geç Trimester İzole İntrauterin Büyüme Geriliğinde maternal NGAL Seviyesi

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ABSTRACT

Aim: Intrauterine growth restriction (IUGR) is the inability of the fetus to achieve the biologically accessible growth potential. Neutrophil gelatinase assosiated lipocalin (NGAL) is synthesised from the cell under stress. Infection, inflammation (synthesised from secondary granules of activated neutrophils), ischaemia, neoplastic transformation are conditions that increase NGAL expression. Our current study aims to investigate the relationship between the isolated IUGR in the third trimester and maternal serum NGAL.

Materials and Methods: This prospective case-control study included a total of 88 pregnant women who were between the 24th and 39th gestational weeks and who applied to the Lokman Hekim University Ankara Hospital Gynaecology and Obstetrics Department between 2020 March-2022 October. The study group consisted of 41 pregnant women who were diagnosed with Isolated IUGR with Estimated Fetal Weight (EFW) <10th percentile. The control group consisted of 47 low-risk uncomplicated pregnant women, matched with the study group in terms of gestational week, and with EFW between 10th and 90th percentiles. Demographic data, clinical findings, fetal doppler parameters, and obstetric-neonatal outcomes were evaluated. Maternal serum NGAL levels were measured by ELISA (Enzyme-Linked Immunosorbent Assay) method and compared between the groups.

Results: Maternal serum NGAL level was found to be significantly higher in IUGR group compared to the control (7,765 vs 3.781, p<.001, respectively). There was a negative correlation between maternal serum NGAL level and duration of pregnancy, the weight gain during pregnancy, birthweight, fetal abdominal circumference measurement and cerebroplacental ratio (r=0.18, p=0.03; r=0.17, p=0.04; r=0.37, p<0.001; r=0.35, p<0.001; r=0.27, p=0.001, respectively). Binary Logistic Regression Analysis showed that maternal serum NGAL level is an independent estimator of IUGR [OR %95 CI: 8.33 (3.22_25.01)].

Conclusion: High levels of maternal serum NGAL in pregnancies with isolated IUGR was consistent with the role of NGAL in inflamation pathways and with the increased risk of placental vasoconstriction. Maternal NGAL level can be analysed to predict isolated IUGR and precautions can be taken.

Keywords: Intrauterine growth restriction, NGAL, placenta

ÖZ

Amaç: İntrauterin Büyüme geriliği (IUGR), fetüsün biyolojik olarak erişilebilir büyüme potansiyeline ulaşamamasıdır. Nötrofil gelatinaz assosiate lipocalin (NGAL) stres altındaki hücreden sentezlenir. Enfeksiyon, inflamasyon (aktive nötrofillerin sekonder granüllerinden sentezlenir), iskemi, neoplastik transformasyon NGAL ekpresyonunun arttıran durumlardır. Mevcut çalışmamız, üçüncü trimesterde izole IUGR ile maternal serum NGAL arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Bu prospektif vaka-kontrol çalışmasına toplam 88 gebe dahil edilmiştir. 24'üncü ve 39'uncu gebelik haftaları arasında olan ve Lokman Hekim Üniversitesi Ankara Hastanesi Kadın Hastalıkları ve Doğum bölümünde, 2020 Mart-2022 Ekim tarihleri arasında çalışma grubu, Tahmini Fetal Ağırlığı (EFW) <10. persentil olan İzole IUGR tanısı almış 41 hamile kadından oluşmaktadır. Kontrol grubu, gebelik haftası açısından çalışma grubu ile eşleşen ve EFW'si 10. ve 90. persentiller arasında olan 47 düşük riskli komplikasyonsuz gebe kadından oluşmuştur. Demografik veriler, klinik bulgular, fetal Doppler parametreleri ve obstetrik-neonatal sonuçlar değerlendirilmiştir. Maternal serum NGAL düzeyleri ELISA (Enzyme-Linked Immunosorbent Assay) yöntemi ile ölçülmüş ve gruplar arasında karşılaştırılmıştır.

Bulgular: Maternal serum NGAL düzeyi IUGR grubunda kontrole kıyasla anlamlı derecede yüksek bulunmuştur (sırasıyla 7,765 vs 3.78, p<0.001). Anne serum NGAL düzeyi ile gebelik süresi, gebelik sırasındaki ağırlık, doğum ağırlığı, fetal karın çevresi ölçümü ve serebroplasental oran arasında negatif bir ilişki vardı (sırasıyla r=0,18, p=0,03; r=0,17, p=0,04; r=0,37, p<0,001; r=0,35, p<0,001; r=0,27, p=0,001). İkili Lojistik Regresyon Analizine göre maternal serum NGAL düzeyi ile IUGR'nin tahmin edilebileceği gösterildi. [OR %95 CI: 8.33 (3.22_25.01)].

Sonuç: İzole IUGR'li gebeliklerde maternal serum NGAL düzeyinin yüksek olması, NGAL'in inflamasyon yollarındaki rolü ve plasental vazokontrüksiyon riskindeki artış ile uyumludur. Maternal NGAL düzeyine bakılarak izole IUGR'yi tahmin edip önlemler alınabilir.

Anahtar Kelimeler: İntrauterin büyüme geriliği, NGAL, plasenta

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INTRODUCTION

Intrauterine growth restriction (IUGR) is the inability of the fetus to achieve the biologically accessible growth potential due to an underlying pathology. IUGR may result from fetal, maternal, placental, genetic, or some metabolic factors (1,2). Intrauterine growth restriction (IUGR) is the inability of the fetus to achieve the biologically accessible growth potential due to an underlying pathology. IUGR may result from fetal, maternal, placental, genetic or some metabolic factors. It is an important cause of fetal and neonatal morbidity and mortality. It is defined as fetal growth rate which is lower than normal according to the growth potential of the baby (3). IUGR may be classified as early or late according to the time of diagnosis and as symmetrical or asymmetrical according to the fetal growth pattern. The pathogenesis of IUGR is not well-defined; however, the underlying physiopathological processes may alter utero-placental circulation and/or impair fetal oxygenation and nutrient exchange (4,5).

Placental insufficiency is considered to be an important factor in the etiology of IUGR. Placental dysfunction resulting from inadequate remodelling of the uteroplacental circulation and consequenthy may lead to vasoconstriction, decreased oxygen transfer to the fetus and consequently restricted fetal growth (6,7).

NGAL (Neutrophil gelatinase assosiated lipocalin), a monomeric protein that has proven its importance as an early, diagnostic biomarker in many recent studies, especially in acute kidney injury, was first identified as a protein bound to the gelatinase of neutrophils. NGAL is a member of the lipocalin (lipocalin2 - lcn2) superfamily, which was thought to function as extracellular transport proteins (e.g. retinol binding protein, fattyacidbinding protein), but recently it has become clear that its biological functions show a great functional diversity, ranging from olfaction to prostaglandin synthesis. NGAL is synthesised from the cell under stress. Infection, inflammation (synthesised from secondary granules of activated neutrophils), ischemia, neoplastic transformation are conditions that increase NGAL expression. NGAL is expressed by human neutrophils and various epithelial cells in response to inflammation, ischaemia and neoplasia (8,9,10).

In our study, we analysed maternal NGAL levels in intrauterine growth restriction.

MATERIALS AND METHODS

Fetal percentiles and study groups. This study is a prospective case-control study, including 88 pregnant women between 24th and 39th weeks of gestation who applied to the, Lokman Hekim University Ankara Hospital Gynaecology and Obstetrics Department Ankara, Turkey, between 2020 March-2022 October. We evaluated the previous routine pregnancy follow-up data of all participants from the beginning of the pregnancy to the inclusion of the current study and we determined if there were any fetal or maternal morbidity which required the patient to be excluded. Patients <18 or >40 years of age, with multiple pregnancies, oligo or polyhydramnios, autoimmune diseases, teratogenous drugs (i.e. cyclophosphamide, valproic acid and antithrombotic drugs), chronic hypertension, cardiovascular disease, hepatic-renal disorders, thyroiddys function, Type 1 or Type 2 DM, gestational Diabetes Mellitus (GDM), metabolic syndrome, preeclampsia, eclampsia, HELLP syndrome, renal diseases, placenta or umbilical cord anomalies, fetal chromosomal anomaly or fetal congenital malformations were excluded from this study. The study group consisted of 41 pregnant women at the 3rd trimester (between the 24th and 39th gestational weeks) with Estimated Fetal Weight (EFW) below 10th percentile and no maternal or fetal morbidity other than IUGR (isolated IUGR). The Control Group consisted of 47 pregnant women whose pregnancies were uncomplicated and appropriate for Gestational Age (AGA) with EFW between 10th and 90th percentiles. The study (IUGR) and Control (AGA) Groups were compared in terms of maternal serum NGAL levels. Pregnant women included in the Study and Control Groups were selected to match each other in terms of gestational weeks. Informed consents were obtained from all individual participants included in the study. The demographic data including age, gravidity, parity, BodyMass Index (BMI), Weight Gain During Pregnancy (WGDP) and gestational age were noted. The estimation of gestational age was based on ultrasonography performed between 11th and 14th gestational weeks. Pregnancy-related data and ultrasonographic measurements were made simultaneously with the serum sampling at a single visit between 24th and 39th weeks of gestation. BMI was calculated as weight (kg)weight/height (m^2). WGDP was defined as the weight gain from the beginning of pregnancy to the date in which the patient was included in our study. The type of delivery and neonatal outcomes were recorded.

Biochemical assay

Maternal venous blood sample was taken from the antecubital vein after 8 h of fasting to the gel biochemical tubes by using a vacuum system for each patient. Centrifuged at 1000xg for 20 minutes within 1 hour and stored at -20°C until the day of the study. The serum sampling was performed at the same single visit with the obstetric ultrasonographic evaluation. Serum samples were collected and stored according to the recommendations of the Enzyme- Linked Immunosorbent Assay (ELISA) kit that we planned to use (Neotropil gelatinaze associated lipocalin human elisa kit

cloud clone (USCNK) marka).Therefore in order to standardize the effect of the storage time on NGAL level, serum samples of the Study Group members were collected on the same day with the matching Control this situation is related to the storage period of serum samples, we preferred to use the most suitable ELISA kit for our storage conditions.

Ultrasonographic measurements

Ultrasonographic measurements were performed by using Toshiba Aplio 500 (Toshiba Medical SystemsCorp., Tokyo, Japan). Fetal biometric measurements (Biparietal diameter (BPD), Abdominal Circumference(AC), Femur length (FL), amniotic fluid index (AFI) measurement), fetal respiratory-tonus movements and Pulsatility Indices (PI) of Middle Cerebral Artery (MCA) and Umbilical Artery (UA), and presence of early diastolic notch in bilateral UterineArtery (UtA) were evaluated. For all patients by the same experienced physician. Cerebroplacental Ratio (CPR) was calculated as MCA PI/UA PI; and EFW was calculated through BPD, AC and FL measurements. All ultrasonographic measurements were performed in accordance with the recommendations of ISUOG guidelines (11).

Statistical analysis

Statistical analysis was carried out by using SPSS softwareversion 26.0 (SPSS Inc., Chicago, IL). The variables were investigated by using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they are normally distributed. Descriptive statistics were given as Mean ± Standard Deviationor Median(Minimum–Maximum) for continuous variables, and number of cases (n) and (%) for categorical variables. Mann–Whitney U and Chi-Squaretests were used to compare these variables. Descriptive analyses were presented by using Mean ± Standard Deviation for the normally distributed variables, and Student'st-test was used to compare these variables. Spearman'scorrelation analysis was used to determine whether there was a significant relationship between continuous variables. In terms of the relationship between IUGR and maternal serum NGALlevel, confounding factors were evaluated by binary logistic regression analysis. In order to determine whether NGALwas a statistically significant determinant in the estimation of IUGR, 95% Confidence Intervalan the area under the curve (AUC) were calculated through ROC (receiver-operating characteristics) Analysis by using Medcalc V13.The sensitivity, specificity, positive and negative predictive values of the NGAL at this value were calculated. Ap-value of <05 was considered statistically significant. G Power version 3 software was used in the power analysis of the study (12).

Ethics committee approval numbered 2022/1 was obtained from Lokman Hekim University.

RESULTS

Maternal NGAL level was measured in 100 pregnant women (50 patients for each group) admitted our hospital for a routine follow-up at the third trimester over seven months. Seven patients in the study group and 5 patients in the control group were excluded from the study for various reasons including quitting the antenatal follow-up and development of obstetric complications during the course of present pregnancy after our examination and fetal anomaly detected at birth. In the final analysis, 88 pregnant women with the diagnosis of IUGR (n=41) and AGA pregnancies (n=47) completed antenatal follow-up in our hospital. Patients' demographic characteristics and clinical features are demonstrated in Table 1. There was no significant difference in terms of age, gravidity, parity, BMI, BUN,

Table 1. Demographic characteristics and clinical features.

Variables	IUGR (n=41)	AGA (n=47)	p
Maternal age (year) Mean ± SD	27.21 ± 5.36	26.1 ± 5.97	.23
Gravidity Median (Min-Max)	2 (1-5)	1 (1-8)	.53
Parity n (%)			
1	19(59)	12(45)	
2	10(29)	10(35)	
3 ve üzeri	3 (12)	6(20)	
BMI (kg/m2) Mean ± SD	28.21 ± 4.62	29.5 ± 4.27	.26
WGDP (kg) Mean ± SD	9.53 ± 4.69	11.33 ± 5.25	.04.67
Gestational age (day) Mean ± SD	238 ± 25	234 ± 24	.72
SBP (mm/Hg)	116.17 ± 12.32	114.78 ± 15.72	.128
DBP (mm/Hg)	75.52 ± 9.34	72.48 ± 8.67	.273
AST (U/L)	21 ± 3.27	22 ± 3.95	.223
ALT (U/L)	19 ± 3.58	20 ± 3.14	.274
Cre(µmol/L) 69-71	69 ± 6.73	71 ± 7.45	.121
Uric acid (µmol/L)	305 ± 16.56	312 ± 18.27	.217

WGDP: Weight gain during pregnancy; AGA: Appropriate for gestational age; BMI: Body massindex, IUGR: Intrauterine growth restriction. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure
p< .05 was considered statistically significant.

Table 2. Maternal NGAL level, ultrasonographic findings, obstetric and neonatal outcomes.

Variables	IUGR (n =41)	AGA (n = 47)	p
Maternal NGAL level (ng/ml) Median (Min–Max)ng/ml)	7,765 (2.38-5)	3.781 (3.54-5)	<.001
BPD value (day) Median (Min–Max)	216 (139-265)	237 (160-265)	<.001
AC value (day) Mean ± SD	205 ± 24	231 ± 25	<.001
FL value (day) Median (Min–Max)	216 (139-265)	237 (167-272)	<.001
MCA PI Mean ± SD	1.57 ± 0.41	2.85 ± 0.35	<.001
UA PI Median (Min–Max)	1.04 (0.48-2.43)	0.90 (0.53-1.24)	<.001
CPR (MCA PI/UA PI) Mean ± SD	1.47 ± 0.58	2.08 ± 0.47	<.001
CPR <1 n(%)	28(30)	-	
Uterine Arter Early Diastolic Notch			
Right n (%)	19 (39)	10 (14)	.001
Left n (%)	12 (31)	8 (11)	.007
Bilateral n (%)	10(26)	4 (6)	.01
Gender			
Female n (%)	21 (59)	27 (54)	
Male n (%)	20(41)	20 (46)	
Birthweight (g) Mean ± SD	1970 ± 659	3280 ± 378	<.001
Apgarscore in 1st minute<7 n(%)	16 (34)	4 (6)	<.001
Type of delivery1			
Vaginal n (%)	16 (37)	47 (68)	
C-section n (%)	25 (63)	22 (32)	
C-sectionindication	<.001		
Cephalo-pelvic disproportion n (%)	4 (7)	14(36.5)	
Previous cesarean n (%)	5 (7)	20 (50)	
Fetal distress n (%)	16 (86)	6(4.5)	<.001
Other n (%)	–	7(9)	

IUGR: Intrauterine growth restriction; AGA: Appropriate for gestational age; BPD: Fetal biparietal diameter; AC: Fetal abdominal circumference; FL: Fetal femur length; CPR: Cerebro placental ratio; MCA PI: Middle cerebral artery pulsatility index; UA PI: Umbilical artery pulsatility index. p< .05 was considered statistically significant.

cre, AST, ALT pregnancy between conclusion. Our study is important to reveal the relationship between maternal serum NGAL level and IUGR in terms of its design in which a large group of patients were involved and the obstetric co-morbidities effecting the NGAL level were excluded.

In the post-hoc power analysis, the power of the study was found to be 0.89 with a 0.5 effect size and 0.05 error rate, for 88 participants consisting of 41 isolated the two groups (p > 05) (table I)

The weight gain during pregnancy (WGDP) was significantly lower in IUGR Group (p=0.04). Table 2 shows maternal NGAL level, ultrasonographic findings, obstetricand neonatal outcomes. Maternal serum NGAL level was found to be significantly higher in IUGR Group compared to the AGA Controls (7,765 vs 3.781, p<001, respectively). BPD, AC and FL measurements, and doppler parameters (MCA PI, UA PI and CPR) were significantly lower in IUGR Group (p < 001). The most common indication for C-section in the IUGR Group was fetal distress (p < 001).

According to Spearman's Correlation Analysis, there was a significant, negative, and weak correlation between UA PI andmaternal serum NGALlevel (r= –0.30, p < .001). A statistically significant, negative, very weak/weak correlation was observed between the WGDP, birthweight, gestational age, AC value and CPR, and maternal serum NGAL level (r = 0.16, p = .03; r =0.35, p < .001; r = 0.17, p =.02; r =0.34, p < .000; r= 0.26, p =.001, respectively) (Table 3).

Table 3. Correlation between maternal serum NGAL leveland IUGR related parameters.

Variables	r	p
BMI (kg/m2)	0,14	.08
Age (year)	-0.01	.80
Parity (n)	0.09	.21
WGDP(kg)	0.16	.03
Birth weight (g)	0.35	<.001
Gestational age (day)	0.17	.02
AC value (day)	0.34	<.00
CPR (MCA PI/UA PI)	0.26	.001
UA PI	-0.29	<.001
MCA PI	0.13	.07

p< 0.05 was considered statistically significant. AC: Abdominal circumference; MCA PI: Middle cerebral artery pulsatility index; UA PI: Umbilical artery pulsatility index; CPR: Cerebroplacental ratio; BMI: Body mass index; WGDP: Weight gain during pregnancy.

DISCUSSION

Our study is important to reveal the relationship between maternal serum NGAL level and IUGR in terms of its design in which a large group of patients were involved and the obstetric comorbidities affecting the NGAL level were excluded. Our data suggests that higher maternal serum NGAL levels in isolated IUGR pregnancies may contribute to the pathogenesis of longterm results of IUGR as inflammation and related placental hypoperfusion. According to our study, maternal NGAL elevation can be considered as an indicator of placental inflammation and hypoperfusion.

In the present study, maternal serum NGAL level was found to be significantly lower in IUGR pregnancies compared to the uncomplicated AGA pregnancies. Doppler parameters have diagnostic and prognostic value in IUGR. UA Doppler is extremely useful in determining these verity of hypoxia and predicting the neonatal outcomes. In this aspect, even though the MCA Doppler finding sare not solely sufficient at the evaluation of IUGR, CPR (MCA PI/UA PI) is important to reveal these verity of the brain-sparing effect in assessing both feto-placental and fetal cerebral blood flows. Our current study revealed a significant negative correlation betweenthe UA PI, CPR, birthweight and NGAL level which suggests that NGAL may be a promising molecule in terms of perinatal outcomes. The data indicated that IUGR pregnant women with an NGAL level higher than AGA (13).

In existing studies, it was determined that oxidative stress occurring in pre-eclampsia, essential hypertension or pregnancy-induced hypertension may be the cause of IUGR (14). Placental dysfunction is the result of inadequate remodeling of the uterine and placental spiral arteries. Further sustained vasoconstriction of these arteries results in decreased oxygen transfer to the fetus and subsequent fetal growth (15). The villous trophoblasts of the terminal villi and the blood vessels on the fetal side form a finely differentiated vascular network to provide the fetus with adequate oxygen and substances for fetal growth. Arterial circulation in the placenta is regulated solely by local signals such as pressure and flow. Abnormal maternal-fetal circulation due to poor placentation in early pregnancy renders the placenta hypoxic, and in response, a series of pro-inflammatory factors are released from the placenta that damage maternal endothelial cells; as a result, vascular resistance increases, resulting in a disruption of the placental angioarchitecture, which can lead to the development of maternal hypertension and abnormal fetal growth (16).

NGAL has been regarded as an acute-phase protein because its blood level is increased under inflamation. Plasma NGAL is known to be elevated in diabetic patients due to renal dysfunction and inflammation (17). Furthermore, NGAL plays a role in the development of anemia by inhibiting erythropoiesis in patients with systemic inflammation (18).It is an adipocytokine that is highly expressed in adipose tissues and implicated in various metabolic and inflammatory diseases (19). It has been reported in previous studies that NGAL levels were increased in preeclampsia and SGA infants of mothers with preeclampsia (20,21,22). NGA iregulates cell migration and apoptosis and plays a role in epithelial cell damage (23). Studies have shown that there is no significant change in NGAL levels between trimesters (24).

Although mothers with preeclampsia were not included in our study group, the fact that NGAL levels were high and that it caused IUGR by affecting Doppler parameters suggests that the increase in NGAL may effect uterine artery bloodflow. From a different perspective; when it is accepted that IUGR develops due to placental insufficiency, it is estimated that NGAL enzyme may increase in response to the infection, based on the view that placental insufficiency may be caused by placental infection. We can predict the development of IUGR by checking the maternal NGAL level in the first trimester.

Kamianowska et al. Noticed that urinary NGAL concentration increased in newborns with intrauterine growth restriction (25). Inaddition, Soni et al. Observed significantly smaller kidneys in the newborn piglets they examined and also showed high levels of MDA in kidney tissue and NGAL in serum samples(26).

Indeed, there is a study that determined that newborn NGAL level may have a predictive role in predicting babies with a birthweight of 1500 g and below without majör congenital anomalies or sepsis (27).

Serum NGAL levels in the first trimester of pregnancy were positively associated with an increased risk of GDM after adjustment for potential cofounding factors. The risk prediction model for GDM constructed by using serum NGAL levels in the first trimester of pregnancy achieved excellent performance (28).

CONCLUSION

The shortcoming of our study was not looking at cord and newborn NGAL levels. The results obtained from the study evaluating maternal, cord and newborn NGAL levels together in IUGR maydeterminethatmaternal NGAL level can be a biomarkerthat can be used to predict IUGR or predict the prognosis of babies with IUGR.

Ethics Committee Approval: Ethics committee approval numbered 2022/1 was obtained from Lokman Hekim University.

Conflict of intereststatement: None

Author contribution: ÖÖÇ: Methodology, datacollection, writing, editing, FB: technicalassistance, datacollection, correction, analysis. SA: Analysis, datacollection

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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The Forty Threshold: Does Maternal Age Impact the Mode of Delivery?

Kırk Eşiği: Maternal Yaş Doğum Şeklini Etkiler mi?

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ABSTRACT

Aim: The global trend of delayed childbearing has led to an increase in pregnancies among women of advanced maternal age (AMA), particularly those aged ≥ 40 years. This demographic shift is associated with maternal and perinatal adverse outcomes which may lead to high cesarean section (CS) rates. To evaluate and compare CS rates of women aged 40 years and older and those under 40 years, delivering at a tertiary referral center.

Material and Methods: All singleton live births at Ankara Bilkent City Hospital between years 2019 – 2025 were analyzed for this retrospective study. Patients were divided into two groups as: women aged ≥40 years (AMA group) and women <40 years (control group). The data were extracted from electronic medical records. Maternal age, delivery mode, and neonatal intensive care unit (NICU) admission, neonatal sex were recorded.

Results: A total of 44,075 singleton live births were recorded. Whereas 3,805 (8.63%) were to women aged ≥40 years and 40,270 (91.37%) were to women <40 years. The median age of the AMA group was 44 (40-62) years. The CS rate was found significantly higher in the AMA group when compared to the control group (69.57% vs. 53.56%, p< 0.001). In addition, NICU admission was significantly higher in the AMA group.

Conclusion: AMA is in association with a significant increase in CS delivery rate. Age-specific counseling and individualized delivery planning for women of advanced maternal age should be considered.

Keywords: advanced maternal age; cesarean section; obstetric outcomes

ÖZ

Amaç: Gebelik yaşının giderek ertelenmesiyle birlikte, ileri anne yaşı (İAY) olan, özellikle ≥40 yaşındaki kadınlarda gebeliklerde artış gözlemlenmektedir. Bu demografik değişim, anne ve perinatal sonuçlarda olumsuzluklarla ilişkilidir ve sezaryen doğum oranlarının yükselmesine neden olabilmektedir. Tersiyer bir başvuru merkezinde doğum yapan ≥40 yaşındaki kadınlar ile 40 yaş altındaki kadınların sezaryen oranlarının değerlendirilmesi ve karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmada, 2019–2025 yılları arasında Ankara Bilkent Şehir Hastanesi'nde gerçekleşen tüm tekil canlı doğumlar analiz edilmiştir. Hastalar iki gruba ayrılmıştır: ≥40 yaş olan kadınlar (İAY grubu) ve <40 yaş olan kadınlar (kontrol grubu). Veriler elektronik hasta kayıt sisteminden elde edilmiştir. Anne yaşı, doğum şekli, yenidoğan yoğun bakım ünitesi (YYBÜ) yatışı ve yenidoğan cinsiyeti kaydedilmiştir.

Bulgular: Toplam 44.075 tekil canlı doğum kaydedilmiştir. Bu doğumların 3.805'i (%8,63) ≥40 yaş kadınlarda, 40.270'i (%91,37) <40 yaş kadınlarda gerçekleşmiştir. İAY grubunun medyan yaşı 44 (40–62) iken, kontrol grubunun medyan yaşı 26'dır (15–39). Sezaryen oranı, İAY grubunda kontrol grubuna göre anlamlı şekilde daha yüksek bulunmuştur (%69,57'ye karşı %53,56, p<0,001). Ayrıca, YYBÜ'ye yatış oranı da İAY grubunda anlamlı olarak daha fazlaydı.

Sonuç: İleri anne yaşı, sezaryen doğum oranlarında belirgin bir artış ile ilişkilidir. Bu nedenle, ileri yaş gebeler için yaşa özgü danışmanlık ve bireyselleştirilmiş doğum planlaması dikkate alınmalıdır.

Anahtar Kelimeler: İleri anne yaşı, obstetrik sonuçlar, sezaryen

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INTRODUCTION

Globally there is an increasing number of women initiating pregnancy later in life due to educational, and social factors which led women to a significant postponement of childbearing age. A notable rise in pregnancies at even the age of 40 and older is seen. This has influenced health policy and obstetric practice.

Advanced maternal age (AMA), is generally defined as 35 years and older (1). Over the last 20 years, the rates of pregnancies and births at AMA have nearly doubled globally. Nearly one fifth of the all pregnancies in United States were shown to be in women 35 years and older (2). This demographic shift led to new risk profiles and management strategies in obstetric and neonatal outcomes. Although, AMA is generally defined as 35 years and older; in obstetric practice, recent studies have divided the patient groups as 35-39 years, 40-44 years as possible pregnancy related risks are associated with advancing age, and women aged 40 and above constitute a distinct high-risk group (3). Pregnancies achieved through assisted reproductive technologies (ART) have also increased, and despite ethical issues, pregnancies achieved through donation and over the age of 50 are now common (4).

AMA has been shown to be associated with increased pregnancy complications such as hypertensive disorders, gestational diabetes mellitus, higher cesarean section (CS) delivery rates (5). Neonatal outcomes are of clinical importance in AMA. Preterm birth, intrauterine fetal growth restriction (IUGR) were observed to a high extent in AMA patients thereby increasing the CS rates (6).

CS delivery rates have been rising rapidly worldwide. World Health Organization (WHO) recommends an ideal cesarean rate of 10–15% (7). However, this rate exceeds 50% in many countries (8) (9). Factors beyond medical indications such as medicolegal concerns, and high patient expectations significantly also contribute to higher CS rates in AMA patients.

There is a lack of detailed data on the birth outcomes of AMA pregnancies in Turkey. Therefore, this study aims to evaluate the impact of AMA on CS rates in pregnant women aged ≥40 years versus those under 40.

MATERIALS AND METHODS

This retrospective, cross-sectional study was conducted at the Department of Obstetrics, Ankara Bilkent City Hospital—a tertiary referral center. The study reviewed all singleton live birth deliveries between the years 2019-2025. Ethical approval for the study was obtained from the Institutional Ethics Committee (Approval Number: 2-25-1357, 06.25).

The maternal age at the time of delivery was recorded. Patients were divided into two groups as:

- Advanced Maternal Age group: Women aged ≥40 years
- Control Group: Women aged <40 years.

Multiple pregnancies, stillbirths, and patients with incomplete records were excluded from the study. Detailed indications for cesarean section were not consistently recorded in the hospital's electronic medical system and therefore were not included in the analysis.

All data were extracted from the hospital's electronic medical system. The following variables were collected and compared between the groups:

- Demographic characteristics: maternal age.
- Mode of delivery: vaginal or cesarean section
- Neonatal gender, neonatal intensive care unit (NICU) admission
- Number and percentage of cesarean sections per group

Statistical Analysis

IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analyses. Data were analyzed using descriptive statistics. Categorical variables (e.g., mode of delivery, gender distribution) were presented as frequencies and n (%). Comparative analysis between groups was conducted using the Chi-square test (χ^2). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 44,075 live singleton births were recorded over six years at Ankara Bilkent City Hospital. Among these live births 3,805 births (8.63%) occurred in women aged ≥40 years whereas 40,270 births (91.37%) occurred in women under 40 years of age. The median age of the AMA group was 44 (40-62) years. The median age of the control group was 26 (15-39) years. There were 29 patients detected to have singleton live births under the age of 18.

Table 1. Cesarean Section Rates by Maternal Age Group

Group	Cesarean Section (n, %)	p value
AMA (n=3,805)	2,647 (69.57%)	<0.001
Control (n=40,270)	21,570 (53.56%)	

Abbreviations: AMA: advanced maternal age; n: number; %: percentage.
A p-value <0.05 was considered statistically significant.

Table 2. Comprehensive Neonatal Outcomes by Maternal Age Group

Group	Male Births (n, %)	Female Births (n, %)	p value (Sex)	NICU Admissions (n, %)	p value (NICU)
AMA	2,049 (53.81%)	1,759 (46.19%)	0.17	495 (13.01%)	<0.001
Control	21,211 (52.60%)	19,116 (47.40%)		3,218 (7.99%)	

Abbreviations: AMA: advanced maternal age; n: number; %: percentage.
A p-value <0.05 was considered statistically significant.

The overall CS rate in the whole study population was 54.82%. A statistically significant difference was observed between the groups in terms of CS rates. In the AMA group, 2,647 of 3,805 births (69.57%) were delivered via CS. In the control group, 21,570 of 40,270 births (53.56%) were delivered via CS (p <0.001) (Table 1).

The distribution of fetal gender by maternal age is presented in Table 2. There was no significant difference in gender distribution between the groups (p = 0.17). However, NICU admission of the AMA group (13.01 %) was found to be significantly higher than the control group (7.99 %) (p <0.001).

DISCUSSION

In this study, the impact of AMA (≥40 years) on CS delivery rates were comprehensively analyzed. This study's findings demonstrate that the CS rate was shown to be significantly higher among women aged 40 and above and NICU admission of the AMA group was higher.

The CS rate in women aged 40 and over was found to be 69.6%, compared to 53.6% in pregnant women <40 years. This is consistent with the literature published in the past decade (9). AMA was reported to be a significant risk factor for cesarean delivery Diabelková et al., Lin et al., and Sidik & Suharyo have also highlighted that complications such as hypertension, diabetes, placenta previa, fetal malpresentation, and previous cesarean history become more common with increasing age, thereby increasing the likelihood of CS (10-12).

The increase in CS rates among AMA can be attributed to both biological and healthcare related factors. Reduced uterine contractility, placental dysfunction, and myometrial structural alterations have been shown as age-related changes (13). Additionally, the higher prevalence of comorbidities such as obesity, chronic diseases in this group of pregnant women supports the need for emergency or elective CS delivery. There is also a tendency toward more frequent CS in women who conceived via infertility treatments (14).

Social, cultural, and healthcare system factors also play a role in the high CS rates. Medicolegal concerns, and increased anxiety regarding delivery in AMA leads to more frequent elective CS (15). Additionally, in tertiary referee hospitals such as ours that manage high-risk pregnancies, clinical routines may further influence cesarean decision-making. These all explain the high CS rates of the current study.

In addition to biological and obstetric risk factors, psychosocial and cultural influences, including heightened maternal anxiety, family preferences, and sociocultural perceptions of childbirth safety, may contribute to higher elective cesarean section rates in this age group. Previous studies in similar populations have reported that these factors, combined with medicolegal concerns, can significantly shape delivery preferences and contribute to the higher CS rates observed in tertiary centers managing high-risk pregnancies.

In Turkey, as in many other countries, delivery decisions for women of advanced maternal age are shaped not only by obstetric risk but also by sociocultural and legal factors. Heightened maternal anxiety, strong family influence, and societal perceptions that cesarean delivery is safer than vaginal birth contribute to increased elective CS rates. Additionally, medicolegal concerns among healthcare providers may lower the threshold for recommending cesarean delivery, particularly in tertiary centers managing high-risk pregnancies.

This is a large, single-center cohort from Turkey, with standardized protocols and robust comparative data on the delivery mode. The results of the study were consistent with the literature, emphasizing that maternal age should be considered a risk factor in delivery planning. However, the retrospective design of the study is the main limitation of this study. Parity, body mass index, socioeconomic status, and ART history which are potential confounders could not be analyzed for all cases, therefore not given as a result. In addition, CS indications could not be detailed, and neonatal outcomes were limited to sex distribution and NICU admission only. The retrospective nature of the study precluded complete data collection for certain potential confounders, including parity, body mass index, and assisted reproductive technology history.

The absence of these variables may have limited our ability to fully adjust for their potential effects on the observed associations Maternal age should be considered in delivery planning, and further prospective research is warranted to clarify the role of age-specific strategies in optimizing outcomes for women of advanced maternal age.

AMA is associated with a significant increase in CS delivery rates. Detailed analysis of CS indications, as well as the influence of psychosocial and cultural factors on birth decisions, should be explored. Maternal age should be a key consideration in birth planning, and guidelines should focus on CS indications to avoid unnecessary interventions. Further studies are needed to reduce CS rates among women of advanced age.

Ethical Approval: This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee. Written informed consent was obtained from all participants prior to their inclusion in the study. Participants had the right to withdraw from the study at any time without consequences. All collected data were anonymized and stored securely to maintain confidentiality.

Consent to Participate: Written informed consent was obtained from all participants after receiving ethics committee approval.

Consent for Publication: This study does not include any identifying patient information, and all data were anonymized to protect participant confidentiality. There are no restrictions or concerns regarding the publication of this study.

Availability of Data and Materials: Patient data utilized in this study are securely stored in the HICAMP® automation system of Ankara Bilkent City Hospital. Data can be accessed upon reasonable request, provided that participant confidentiality is strictly maintained.

Competing Interests: The authors declare that they have no competing interests related to this study.

Permission to Reproduce Material from Other Sources: This study does not include any reproduced material from other sources that requires permission.

Clinical Trial Registration: This study is not a registered clinical trial.

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Are There Any Prognostic Parameters in Pregnant Women with COVID-19? A Cross-Sectional Research

COVID-19'lu Gebe Kadınlarda Herhangi Bir Prognostik Parametre Var Mı? Kesitsel Bir Araştırma

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ABSTRACT

Aim: The aim of this study is to investigate the pre- and post-treatment changes in mean platelet volume (MPV) and other laboratory markers in patients diagnosed with COVID-19.

Material and Methods: We retrospectively evaluated 169 pregnant COVID-19 patients who were admitted to a tertiary care hospital between March 2020 and December 2020. Full blood counts and biochemistry parameters, including C-reactive protein (CRP), ferritin, d-dimer, and procalcitonin were collected on admission and discharge. In addition, chest computed tomography (CT) images, intensive care unit (ICU) requirements, and patients' temperature, oxygen saturation, and heart rates were recorded. Changes in laboratory parameters before and after treatment, as well as the relationships between laboratory parameters and clinical and radiological findings at the time of admission, were evaluated.

Results: Statistically significant differences were observed in the mean pre- and post-treatment values of CRP, D-dimer, MPV, and hemoglobin, as well as in procalcitonin, leukocyte, lymphocyte, and monocyte counts, and the eosinophil-to-monocyte ratio ($p<0.001$). Significant associations were also found between MPV and oxygen saturation, the need for intensive care, and variations across trimesters ($p<0.05$). Moreover, CRP, D-dimer, procalcitonin, and PCR results showed significant correlations with thoracic CT, body temperature, and heart rate measurements ($p<0.05$).

Conclusıon: In pregnant patients diagnosed with COVID-19, significant alterations were observed in certain blood parameters, particularly in MPV. The significant changes in MPV values before and after treatment, along with its positive correlation with the need for intensive care, suggest that MPV may represent a clinically low-cost, simple, practical, and easily applicable marker.

Keywords: COVID-19; mean platelet volume; pregnancy

ÖZ

Amaç: Bu çalışmanın amacı ortalama trombosit hacmi (MPV)'nin ve diğer labaratuvar belirteçlerinin COVID-19 tanılı hastalarda tedavi öncesi ve sonrası değişimini incelemektir.

Gereç ve Yöntemler: Mart 2020 ile Aralık 2020 tarihleri arasında üçüncü basamak bir sağlık merkezine başvuran 169 COVID-19 tanılı gebe hasta retrospektif olarak değerlendirildi. Hastaların yatış (tedavi öncesi) ve taburculuk (tedavi sonrası) anlarında tam kan sayımı ve C-reaktif protein (CRP), ferritin, D-dimer, prokalsitonin gibi biyokimyasal parametreleri kaydedildi. Ayrıca, akciğer bilgisayarlı tomografileri, yoğun bakım gereksinimi ve hastaların ateş, oksijen satürasyonu, nabız hızları kaydedildi. Tedavi öncesi ve sonrası labaratuvar parametrelerindeki değişiklikler ve yatış anındaki klinik ve radyolojik bulguların labaratuvar parametreleri ile olan ilişkileri karşılaştırıldı.

Bulgular: Hastaların tedavi öncesi ve sonrası CRP, D-dimer, MPV ve hemoglobin ortalama değerleri, prokalsitonin, lökosit, lenfosit, monosit sayıları ile eozinofil/monosit oranında istatistiksel olarak anlamlı izlendi.($p<0.001$) MPV ile oksijen satürasyonu, yoğun bakım ihtiyacı ve trimesterlere göre değişiklik açısından istatistiksel olarak anlamlı farklılık izlendi. ($p<0.05$) CRP, D-dimer, proklasitonin ve PCR sonuçları, toraks BT bulguları, ateş ve nabız bulguları ile anlamlı ilişkiler izlendi. ($p<0.05$)

Sonuç: COVID-19 tanılı gebe hastalarda özellikle MPV olmak üzere bazı kan parametrelerinde anlamlı değişiklikler izlenmektedir. Tedavi öncesi ve sonrası MPV değerlerindeki anlamlı değişiklikler ve yoğun bakım ihtiyacı ile olan pozitif korelasyon klinik olarak düşük maliyetli, kolay, pratik ve uygulanabilir olduğunu düşünmekteyiz.

Anahtar Kelimeler: COVID-19; ortalama trombosit hacmi; gebelik

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INTRODUCTION

Coronaviruses are important human and animal pathogens. In late 2019, a new strain of Coronavirus was identified as the cause of a series of pneumonia cases in Wuhan, China. Cases rapidly spread out, first causing an epidemic in China, then a global pandemic. In February 2020, World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) as a pandemic (1). The virus causing COVID-19 was named severe acute respiratory syndrome causing Coronavirus (SARS-CoV-2). In Turkey, the Ministry of Health announced the first case in March 2020.

Data regarding the consequences of previous coronavirus outbreaks (Severe acute respiratory syndrome 1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV)) on pregnancy are limited (2,3). COVID-19 has many features in common with SARS-CoV-1 and MERS-CoV and seems to have similar pathogenic mechanisms (4). Two early meta-analyses suggested that a high percentage of pregnant women with COVID-19, MERS, and SARS experienced adverse pregnancy outcomes. Moreover, there was no evidence for vertical transmission of the virus. However, both meta-analyses suffered from the small number of patients (5).

In addition to its function in hemostasis, platelets play a critical role in the inflammatory response, and their numbers vary depending on the severity of infection (6,7). Platelet size and volume may also change during infections, and this alteration reflects the level of platelet activation. Also Change in mean platelet volume (MPV) level has been identified as a diagnostic and prognostic marker in conditions such as sepsis, infective endocarditis, pneumonia, brucellosis, cellulitis, and acute pyelonephritis (8-10).

The hypothesis of the current study was that COVID-19 might affect platelet volume indices since it causes inflammation as in other viral infections. The aim of the study was to evaluate the relationship between COVID-19 and platelet volume indices and may be effect of treatment on MPV value in pregnant patients with-COVID-19.

MATERIALS AND METHODS

In this retrospective study, we evaluated laboratory, imaging, and clinical records of 169 pregnant women who were referred to the outpatient COVID unit of the emergency department of our hospital between March 2020 (date of first reported COVID-19 case in Türkiye) and December 2020. All of the study participants were admitted to the hospital either with positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test or with pulmonary computed tomography (CT) findings compatible with COVID-19. The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Gazi Yaşargil Training and Research Hospital (Approval No: 685; Date: 05.03.2021)

All pregnant women diagnosed with COVID-19 with a normal body mass index (BMI) were included in the study irrespective of their pregnancy trimester. Patients who were smokers and had a chronic medical condition, anemia (Hb value<12 fl), whose abnormal platelet count or thrombogenic diseases, diabetes mellitus, gestational diabetes mellitus, hypertension, smoking and drug using as may impact on MPV value were not included the study. Patients who were overweight or obes excluded because some studies indicated that high MPV values were in these people, thus we just included whose BMI 18-25 kg/m^2. we excluded the patients. Finally, 18 patients with greater than >25 kg/m^2 and 9 patients with gestational diabetes meliitus were excluded from 196 pregnant patients with COVID-19.

Additional data including patient age, gravidity, parity and BMI, length of stay in the hospital, intensive care requirement, and vital signs were also collected.

Postpartum results and neonatal scores were not included in the analyses. It has been emphasized that the values of MPV and other inflamatuary markers during pregnancy could be a prognostic marker for COVID-19.

Obstetricians collected nasopharyngeal and oropharyngeal swabs for COVID-19 screening. The swabs were examined using the RT-PCR test. Patients with negative PCR test results were also included in the studysince their pulmonary CT scans were evaluated and deemed consistent with COVID-19 by radiologists.A semi-quantitative CT severity scoring was calculated per each of the 5 lobes considering the extent of anatomic involvement, and radiologists described as follows: 0, no involvement; low severity < 5% and 5–25% involvement, middle : 26–75% severity 51–75% involvement; and severe >75% involvement.

Complete blood count parameters, including white blood cell (WBC), monocyte, eosinophil and lymphocyte counts, MPV, C-reactive protein (CRP), D-dimer and ferritin levels were measured both on admission and at discharge were recorded.

Descriptive statistics were expressed as mean, standard deviation (SD), interquartile range (1st and 3rd quartiles), counts, and percent frequencies depending on the type of the variables. Compatibility of numerical data with normal distribution was tested with the Shapiro-Wilks test. The Wilcoxon signed-rank test was used to evaluate the significance of the change between laboratory parameters on admission and discharge. The relationship between this change and the categorical variables of patients was evaluated using the Mann-Whitney U test and the Kruskal-Wallis test. Spearman's rank

correlation analysis was used to determine the relationship between the changes in parameters and other numerical characteristics of the patients. Statistical significance level was accepted as p <0.05. SPSS 25.0 (Statistical Package for Windows, Chicago, Illinois, USA) was used for data analysis. Logistic regresyon was performed for find prognostic factor.

RESULTS

One hundred and sixty-nine pregnant women with COVID-19 were included in the study (median age 29.5 years). Demographic data are presented in Table 1. Most of the pregnant women were in the third trimester (70.8%)

Table 1. Demographic data of the patients

	N	Mean ± SD	Minimum	Maximum
Age (years)	169	29.5 ±6.2	15	43
BMI (kg/m²)	169	21.6 ± 1.8	18.3	24.8
Gravidity	169	3.3 ±1.5	1	8
Parity	169	1.9 ± 1.3	0	7

BMI: Body mass index

Table 2. Distribution of the patients' baseline parameters

		N	%
Trimester	1 2 3	15 34 119	8.9 20.2 70.8
PCR	Negative Positive	18 151	10.7 89.3
Thorax CT	Mild Moderate Severe	43 35 38	37.1 30.2 32.8
O_2 Saturation	<90 % ≥ 90 %	7 161	4.2 95.8
Body temperature (°C)	<37.5 °C ≥37.5 °C	148 19	88.6 11.4
Pulse rate (/min.)	<100 ≥100	130 37	77.8 22.2
Lopinavir+ Ritonavir	No Yes	76 93	45.0 55.0
Hydroxy chloroquine	No Yes	153 16	90.5 9.5
Oseltamivir	No Yes	161 8	95.3 4.7
LMWH	No Yes	49 120	29.0 71.0
Need for Intensive Care	No Yes	145 24	85.8 14.2
Mortalite	No Yes	166 3	98.23 1.77

CT: Computed tomography, LMWH: Low molecular weight heparin, PCR: Polymerase Chain Reaction,

The distribution of patients according to trimester, vital signs, PCR and thoracic CT findings, as well as the use of antiviral therapy, LMWH, hydroxychloroquine treatment, intensive care unit admission, and mortality are presented in Table 2.

When comparing the laboratory values of patients at hospital admission (pre-treatment) and at discharge (post-treatment), a statistically significant decrease was observed in the mean values of CRP, D-dimer, MPV, and hemoglobin, while procalcitonin, leukocyte, lymphocyte, and monocyte counts as well as the eosinophil/monocyte ratio showed a statistically significant increase (p<0.001). No significant change was observed in ferritin levels (p>0.05) (Table 3).

When the changes in laboratory values before and after treatment were evaluated according to trimester, MPV values decreased at discharge in the first trimester, whereas they increased in the second and third trimesters (p=0.007). This finding indicates that the change observed in the first trimester was significantly different from those in the other trimesters (p=0.007). In addition, the decrease in lymphocyte count was significantly greater in women in the third trimester compared to those in the other trimesters (p=0.016). No significant differences were observed among trimesters for the other parameters (Table 4).

Based on the PCR results before and after treatment, only the changes in CRP were found to be significantly higher in PCR-negative patients (p=0.023) (Table 4).

Table 3. Changes in some laboratory measurements from baseline to after treatment

Parameter	n	Before treatment value (mean)	After treatment value (mean)	p-value
CRP (mg/L)	156	35.567	25.078	**<0.001**
D-dimer (mg/L)	111	825.53	762.30	**<0.001**
Ferritin (µg/L)	123	78.77	94.26	0.717
Procalcitonin (ng/mL)	145	0.16622	0.17719	**<0.001**
MPV (fl)	158	10.196	9.848	**<0.001**
WBC (/mm³)	158	9.0184	9.9941	**0.011**
Lymphocyte (/mm³)	158	1.32895	1.7352	**<0.011**
Hemoglobin (g/dL)	158	11.416	10.978	**<0.001**
Monocyte (/mm³)	161	0.4980	0.6909	**<0.001**
Eosinophil (/mm³)	161	0.3837	0.1065	**<0.001**
Eosinophil/ Monocyte	161	0.0734	0.2089	**<0.001**

*Wilcoxon signed-rank test
CRP: C-reactive protein, MPV: Mean platelet volume, WBC: White blood cell

Table 4. Correlation analysis between clinical and laboratory parameters

Variable	Associated parameter	Direction of correlation	p-value
Trimester	MPV	1. trimester ↓ / 2-3. trimester ↑	**0.007**
Trimester	Lymphocyte	More in the 3rd trimester ↓	**0.016**
PCR	CRP	PCR(-) ↑	**0.023**
Thorax CT	CRP	Mıld CT ↓	**0.022**
Thorax CT	D-dimer	Mıld/Moderate ↓, Severe ↑	**0.037**
Thorax CT	Prokalsitonin	Mıld/Moderate ↓, Severe ↑	**0.023**
Thorax CT	Monocyte	Mıld/Moderate/ Severe ↑	**0.042**
Fever≥37.5°C	CRP, Procalsitonin	↑	**<0.05**
Pulse rate ≥100/dk	CRP, Procalsitonin	↑	**<0.05**
Need for intensive care	CRP, Procalsitonin, MPV	↑	**<0.001 / <0.008 / <0.014**
Age	CRP	↑	**0.013**
Age	WBC	↓	**0.010**
Oxygen saturation	MPV	Saturation ↑ → MPV ↓	**<0.05**

PCR: Polymerase Chain Reaction CRP: C- Reactive Protein MPV:Mean platellet Volume CT: Computer tomography

According to thorax CT findings before and after treatment, changes in CRP were significantly lower in patients with mild CT involvement (p=0.022). While D-dimer levels tended to decrease at discharge in patients with mild and moderate CT findings, they increased in those with severe CT findings (p=0.037). Procalcitonin levels were lower at discharge in mild and moderate cases, whereas they were higher in severe cases (p=0.023). Monocyte counts increased at discharge across patients with mild, moderate, and severe CT findings (p=0.042). No significant differences were observed in relation to oxygen saturation (Table 4).

When evaluated in terms of body temperature and pulse values before and after treatment, changes in CRP and procalcitonin were statistically significant in patients with a fever ≥37.5°C and a pulse rate ≥100/min (p<0.05). Regarding intensive care requirement, changes in CRP (p<0.001), procalcitonin (p<0.008), and MPV (p<0.014) were found to be significantly higher in patients who required intensive care (Table 4).

With increasing age, changes in CRP were found to significantly increase (p=0.013), whereas changes in WBC significantly decreased (p=0.01). No significant age-related correlations were observed for the other laboratory parameters (Table 4)

Another parameter that showed a significant correlation with MPV changes was oxygen saturation. As oxygen saturation increased, MPV changes significantly decreased (p<0.001) (Table 4).

DISCUSSION

This study aimed to investigate the pre- and post-treatment changes in MPV and other laboratory markers in pregnant women with COVID-19, and to examine the associations between post-treatment clinical and radiological findings and these markers.

In this study, changes in MPV and other hematological parameters were comprehensively examined in pregnant women diagnosed with COVID-19. Our findings demonstrated significant decreases in CRP, D-dimer, MPV, and hemoglobin levels at discharge, while procalcitonin, leukocyte, lymphocyte, monocyte counts, and the eosinophil-to-monocyte ratio showed significant increases. Furthermore, significant associations were identified between changes in MPV and oxygen saturation, the need for intensive care, and the duration of hospitalization.

Platelet counts and functions undergo physiological changes during pregnancy. In normal pregnancy, a slight decrease in platelet counts and an increase in platelet volume have been reported (11–14). It has been demonstrated that platelet lifespan shortens, platelet destruction accelerates, and consequently, mean platelet volume (MPV) increases (15). These physiological changes may become more pronounced in pregnant women when additional inflammatory processes such as COVID-19 develop. In recent years, MPV has been investigated as a prognostic biomarker in conditions of inflammation and infection. In children with COVID-19, MPV has been reported to have diagnostic value (16). Furthermore, longitudinal laboratory

data in COVID-19 patients showed that MPV changes may be associated with recovery or deterioration (17). Similarly, MPV alterations have been suggested to be useful in distinguishing disease severity in cases with interstitial pneumonia (18,19). In our study, the increase in MPV particularly in third-trimester pregnancies and its inverse correlation with oxygen saturation support the notion that MPV may be related to disease severity. In patients with pneumonia, MPV elevation has been associated with prognosis, with more pronounced increases observed in those admitted to intensive care (20,21). Likewise, higher MPV levels have been reported to be associated with mortality in severe pneumonia cases (22). Zhong et al. also reported that the MPV-to-platelet count ratio could predict severe pneumonia in COVID-19 patients (23). These findings are consistent with our results and suggest that MPV may serve as a potential marker to predict the need for intensive care in pregnant women with COVID-19."A study comparing 55 pediatric patients with a control group found no statistically significant difference between their CRP measurements. (16) MPV values were found to be significantly higher in the COVID-19 patient group, while lymphocyte counts were significantly lower. A study including 24 patients suggested that procalcitonin and MPV changes (decreases) were predictive of patient recovery (17).

A study that included 30 patients and 30 controls to investigate the relationship between laboratory parameters and interstitial pneumonia in COVID-19 found lower white blood cell, monocyte, and neutrophil counts and higherplatelet counts. Furthermore, COVID-19 patients exhibited higher MPV, lower CRP concentrations, and higher De Ritis ratio. Combined blood cell indices of systemic inflammation were significantly lower in patients with COVID-19. In further analysis, it was found that in the COVID-19 group, neutrophil count, neutrophil/lymphocyte ratio (NLR), derived NLR, systemic inflammation response index, and De Ritis ratio were significantly higher in survivors, while the platelet count was significantly lower in non-survivors (18).

A large meta-analysis in China comprising 2984 COVID-19 patients from 18 studies examined laboratory data after grouping the patients into two categories: severe and non-severe (19). The study found that IL-6 and ferritin levels were higher in the severe disease group. In our study, while changes in ferritin levels were not significant, changes in MPVwere significant. Therefore, we believe that MPV might be as much valuable as other prognostic markers in the monitoring of COVID-19 patients.

Previous studies have shown that MPV alterations may reflect ongoing inflammatory processes and could be valuable in monitoring disease activity (20). An increase in MPV has been reported to be associated with prognosis in patients with pneumonia, with more pronounced elevations observed in those admitted to intensive care units (21). Similarly, higher MPV levels have been linked to mortality in severe pneumonia cases (22). Zhong et al. also demonstrated that the MPV-to-platelet ratio could predict severe pneumonia in COVID-19 patients (23). These findings are consistent with our results and suggest that MPV may serve as a predictive marker for intensive care requirements in pregnant women with COVID-19. Moreover, in our study, the positive correlation between MPV elevation and length of hospital stay indicates that this parameter may not only reflect acute prognosis but also predict prolonged disease course. This observation has also been highlighted in previous studies of pneumonia unrelated to COVID-19 (21,22). In conclusion, this study demonstrates that MPV changes provide important insights into the clinical course of COVID-19 in pregnant women. MPV elevation was associated with intensive care need and decreased oxygen saturation. Our findings suggest that MPV could be a valuable biomarker in predicting disease severity in pregnant women with COVID-19. Furthermore, the easy accessibility of MPV within routine laboratory testing supports its potential clinical utility.

Ethical Approval: The approval for the present study was granted by the Republic of Turkey Ministry of Health. Health Sciences University, Gazi Yaşargil Education and Research Hospital Ethics Board approved the study protocol (decision no: 685, 05.03.2021).

Authorship Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflict of Interest: No conflict of interest was declared by the authors.

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Can Systemic Inflammatory Indices Be Useful in Hypertensive Disorders of Pregnancy?

Gebeliğin Hipertansif Hastalıklarında Sistemik İnflamatuar İndeksler Faydalı Olabilir mi?

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ABSTRACT

Aim: This study aimed to assess the utility of systemic inflammatory indices in predicting and determining the prognosis of hypertensive disorders during pregnancy

Materials and Methods: This cross-sectional and retrospective single-center study involved 101 preeclampsia patients and 203 healthy pregnant women as the control group. Laboratory parameters were evaluated during the first trimester, at the time of diagnosis, and prior to delivery. The indices were calculated using laboratory values: PLR (platelet/lymphocyte), APRI (AST/platelet), SII (neutrophil × platelet / lymphocyte), and SIRI (neutrophil × monocyte / lymphocyte). Subgroup analyses were performed for early- and late-onset preeclampsia, severe and non-severe preeclampsia, and HELLP syndrome.

Results: Indices calculated during the first trimester were insufficient to predict preeclampsia, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Although indices obtained at the time of diagnosis were also limited in predicting poor outcomes, PLR was lower in the preeclamptic group at diagnosis due to changes in lymphocyte counts. APRI was significantly higher in preeclamptic pregnancies, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome prior to delivery ($p<0.001$). Additionally, among patients with HELLP syndrome, a significant increase in SIRI and a decrease in PLR levels were observed before delivery.

Conclusion: Among the inflammatory indices examined, APRI showed a significant elevation prior to delivery in cases of early-onset preeclampsia, severe preeclampsia, and HELLP syndrome. Moreover, in patients diagnosed with HELLP, SIRI increased while PLR decreased significantly. These findings suggest that a late-onset inflammatory response may be linked to increased severity of hypertensive pregnancy disorders.

Keywords: Preeclampsia, inflammation, HELLP, APRI

ÖZ

Amaç: Bu çalışmanın amacı, sistemik inflamatuar indekslerin gebeliğin hipertansif hastalıklarının prediksiyonu ve prognozu açısından faydalı olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Bu kesitsel ve retrospektif tek merkezli çalışma, 101 preeklampsi hastası ve 203 sağlıklı hamile kadından oluşmaktadır. Laboratuvar parametreleri, ilk trimesterde, tanı anında ve doğumdan önce olmak üzere üç ayrı dönemde değerlendirilmiştir. PLR (trombosit/lenfosit), APRI (AST/trombosit), SII (nötrofil x trombosit / lenfosit) ve SIRI (nötrofil x monosit / lenfosit) indeksleri hesaplanmıştır. Bu indeksler ayrıca erken ve geç başlangıçlı preeklampsi, şiddetli ve şiddetli olmayan preeklampsi ile HELLP sendromunu içeren alt gruplarda analiz edilmiştir.

Bulgular: İlk trimesterde hesaplanan tüm indeksler, preeklampsi, şiddetli preeklampsi, erken başlangıçlı preeklampsi ve HELLP sendromunu predikte etme konusunda yetersiz kalmıştır. Tanı anında hesaplanan indeksler de kötü prognozu öngörmede etkili olmamış, ancak PLR'nin preeklamptik grupta kontrol grubuna göre daha düşük olduğu saptanmıştır. Bu farklılık lenfosit değerlerindeki değişikliklerden kaynaklanmıştır. Doğum öncesi dönemde ise APRI hem preeklamptik gebelerde hem şiddetli ve erken başlangıçlı preeklampside hem de HELLP sendromunda anlamlı şekilde yüksek bulunmuştur ($p<0,001$). HELLP sendromu teşhisi alan hastalarda doğum öncesinde SIRI anlamlı olarak artarken, PLR azalmıştır.

Sonuç: İncelenen inflamatuar indeksler arasında, özellikle doğum öncesi dönemde hesaplanan APRI'nin erken başlangıçlı preeklampsi, şiddetli preeklampsi ve HELLP sendromu olgularında anlamlı şekilde yükseldiği saptanmıştır. Ayrıca, HELLP tanısı alan hastalarda SIRI artmış, PLR ise anlamlı düzeyde azalmıştır. Bu bulgular, geç inflamatuar yanıtın gebeliğin hipertansif hastalıklarının şiddetiyle ilişkili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Preeklampsi, inflamasyon, HELLP, APRI

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INTRODUCTION

Preeclampsia is a hypertensive disorder of pregnancy that can lead to serious maternal and fetal complications with multisystem organ involvement. It complicates 2-8% of pregnancies worldwide (1).

Preeclampsia is diagnosed when hypertension develops after the 20th week of gestation and is accompanied by evidence of end-organ dysfunction. Identified risk factors are nulliparity, multiple pregnancies, advanced maternal age, pregnancy with assisted reproductive techniques, maternal comorbidities, obesity (especially pregestational body mass index (BMI) > 30), a history of preeclampsia in the mother and sister, and a previous history of preeclampsia or abruption (2). Although its etiology is still not fully understood, insufficient trophoblast invasion, abnormal placentation, abnormal release of angiogenic factors, and the development of ischemia, inflammation, and atherosclerosis have been implicated (3).

The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) are calculated based on hemogram parameters, which are important mortality markers in cardiovascular diseases and COVID-19 patients (4). The use of systemic immune inflammation index (SII) (neutrophil x platelet/lymphocyte), systemic inflammation response index (SIRI) (neutrophil x monocyte/lymphocyte), and platelet-to-lymphocyte ratio (PLR) indices in predicting preeclampsia has been investigated in some studies considering that preeclampsia is an inflammatory process (5). APRI (AST/platelet) is considered a highly sensitive marker used to predict the degree of liver fibrosis and its progression to cirrhosis (6). Recent studies have reported that it is superior to liver transaminases in predicting HELLP syndrome (7).

In this study, we aimed to investigate how APRI, SIRI, PLR and SII indices changed at the time of diagnosis and before delivery in pregnant women diagnosed with preeclampsia and whether the first trimester indices of the same patients can predict early-onset preeclampsia, severe preeclampsia and progression to HELLP syndrome.

MATERIAL AND METHODS

This retrospective, cross-sectional study was conducted at Ankara Bilkent City Hospital Perinatology Clinic. In this study, 101 patients with preeclampsia as the study group and 203 healthy pregnant women as the control group were included between December 2022 and November 2023. The control group consisted of normotensive pregnant women with similar demographic characteristics. Adolescent pregnancies, maternal age>45 years and pregnant women with chronic systemic diseases were excluded. Demographic data, laboratory parameters, gestational age at diagnosis and delivery were retrieved from the hospital's electronic medical records. This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-23-4881), according to the Helsinki Declarations.

Pregnancy-induced hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured at least 4 hours apart after 20 weeks of gestation. Severe preeclampsia is defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg and proteinuria (≥ 300 mg in 24-hour urine, ≥ +2 with dipstick test, urine protein/creatinine ratio in spot urine ≥ 0.3) or end-organ damage [thrombocytopenia (<100,000/dl), serum creatinine level above 1.1 mg/dl or doubling of serum concentration, doubling of liver transaminases, pulmonary edema, new-onset headache unresponsive to medication, visual symptoms] (2). Early-onset preeclampsia is defined as the onset of the disease before 34 gestational weeks (8). HELLP syndrome is characterized by thrombocytopenia, elevated liver enzymes, and hemolysis (9). The patients were categorized according to the defined diagnostic criteria. Laboratory parameters were studied in three different periods. The patients' complete blood count and biochemical parameters were obtained from the records in the first trimester, at the time of diagnosis and before delivery. Patients were analyzed for the following indices: PLR (platelet to lymphocyte count ratio), APRI (AST to platelet count ratio), SII (neutrophilxplatelet/lymphocyte), and SIRI (neutrophilxmonocyte/lymphocyte). Thereafter, study and control groups were compared for the mentioned parameters at different times. Additionally, preeclampsia groups were divided into subgroups as follows: preeclampsia with/without severe features, early/late-onset preeclampsia and preeclampsia with/without HELLP syndrome. A subgroup analysis was also performed for the comparison of SII, SIRI, PLR and APRI in the first trimester, at time of diagnosis and before delivery.

The statistical analyses were conducted using IBM Inc., Armonk, NY, USA's Statistical Package for the Social Sciences, version 26. Normality was assessed using the Shapiro–Wilk test, and the results indicated that the indexes did not follow a normal distribution. Median and minimum-maximum values were utilized to present descriptive statistics. The other data showed normal distribution, and these data were presented as mean and standard deviation. The Mann-Whitney U was used to compare the parameters between the groups according to distribution. Statistical significance was defined as a two-tailed P value of 0.05 with a 95% confidence interval.

RESULTS

This study included 101 women with preeclampsia and 203 healthy pregnant women as the control group. Of the preeclampsia group, 40 had severe preeclampsia, 61 had non-severe preeclampsia, and 28 were diagnosed with HELLP syndrome. Maternal demographic characteristics and obstetric history are shown in Table 1. When the control and preeclamptic patient groups were compared during the first trimester, at the time of diagnosis, and before delivery, although there was no difference in systemic indices in the first trimester, PLR was lower at the time of diagnosis while platelet count was at normal values. The corresponding data are shown in Table 2. Although PLR was lower in the severe preeclampsia and HELLP groups, no significant difference was observed in the first trimester. Furthermore, in the first trimester, SIRI, SII, and APRI did not differ significantly in the severe preeclampsia and HELLP groups. The corresponding data are shown in Table 3.

In the early-onset preeclampsia group, APRI was significantly higher compared with the late-onset group, and APRI was also higher in the severe preeclampsia group and HELLP group before delivery. SIRI and PLR indices were significantly higher in the HELLP group compared to preeclamptic and healthy pregnant women, but no significant difference was found for SII prior to delivery.

DISCUSSION

The main findings of the present study revealed that SII, SIRI, PLR and APRI indices calculated in the first trimester were insufficient in predicting preeclampsia, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Although the indices calculated at the time of diagnosis were also inadequate in predicting poor prognosis, the PLR was found to be lower in the preeclamptic group at the time of diagnosis compared to the control group. This difference has emerged due to changes in lymphocyte counts. However, the APRI calculated in the pre-delivery period was found to be significantly higher in preeclamptic pregnancies, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Moreover, SIRI, PLR, and APRI levels differed between the HELLP group and the non-HELLP group only before delivery.

Preeclampsia is an important obstetric pathology characterized by hypertension and multisystemic organ involvement. It is also a significant cause of fetal-maternal morbidity and mortality in the world. Many theories have been put forward in its etiology. It has been implicated in the pathophysiology of placental ischemia, which develops as a result of inadequate cytotrophoblastic invasion, inadequate compliance of spiral arteries, endothelial activation and development of atherosclerosis, intravascular inflammation,

Table 1. Maternal demographic characteristics

Variable	Control Group (n=203)	Preeclampsia Group (n=101)	P-value
Maternal age	28.4±5.2	30.8±5.6	**0.001**
Gravida	2.2±1.2	2.8±1.8	0.242
Parity	1.1±1	1.1±1.1	0.573

*All variables were presented as means and standard deviations.

Table 2. Comparison of laboratory values of the control group and the preeclamptic group in three different periods of pregnancy

Variable	Control Group (First Trimester)	Preeclampsia Group (1st Trimester)	P-value (First Trimester)	Control Group (At Diagnosis)	Preeclampsia Group (At Diagnosis)	P-value (At Diagnosis)	Control Group (Prior to Delivery)	Preeclampsia Group (Prior to Delivery)	P-value (Prior to Delivery)
Hemoglobin (g/dL)	12±1.1	12.4±1.2	**0.004**	11.6±1.1	12±1.1	**0.002**	11.8±1.27	11.9±1.44	0.307
Platelet (/mm³)	262280±55234	282720±75569	0.131	240060±66941	248670±94165	0.722	244160±69824	242010±120315	0.119
Wbc (/mm³)	8471±2165	9096±2485	0.082	9535±2064	11147±2974	**<0.001**	10457±2871	12084±3912	0.047
Monocyte (/mm³)	0.46±0.17	0.55±0.22	**0.004**	0.49±1.1	0.52±0.2	0.335	0.52±0.16	0.57±0.28	0.403
Neutrophil (/mm³)	7.22±1.98	7.56±1.22	0.112	7.15±1.85	8.28±2.92	0.011	7.89±2.6	9.21±4	0.303
Lymphocyte (/mm³)	1.88±0.57	1.90±0.59	0.812	1.71±0.5	2.07±0.67	**<0.001**	1.85±0.53	1.88±0.86	0.585
AST (IU/L)	16.7±5	18.3±11	0.945	19.3±6	22.8±9.6	**0.015**	19.8±5.7	60.2±101	**0.001**
ALT (IU/L)	16.7±9.5	19.9±17.1	0.895	15±7.1	19±14	**0.003**	14.9±9.8	56±98	**0.001**
Creatinine (ml/dk)	0.5±0.1	0.6±0.1	**0.035**	0.6±1.3	1.1±3	**<0.001**	0.5±0.09	0.66±0.26	**<0.001**

*All variables were presented as means and standard deviations. WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Comparison of indices with control and preeclamptic groups and between subgroups at 3 different times during pregnancy

Period	Indices	Preeclampsia	Control	P value
First trimester				
	SIRI	1.5 (1.2)	1.3 (1)	0.069
	SII	777 (572)	793 (536)	0.481
	PLR	134 (59)	131 (63)	0.751
	APRI	0.06 (0.03)	0.06(0.03)	0.307
At the time of diagnosis				
	SIRI	1.95 (1.5)	2 (1.29)	0.678
	SII	904 (778)	956 (541)	0.519
	PLR	123 (59)	139 (56)	**0.005**
	APRI	0.09 (0.08)	0.08 (0.04)	0.062
Prior to delivery				
	SIRI	2.3 (2.3)	2.05 (1.25)	0.916
	SII	994 (852)	988 (592)	0.343
	PLR	126(73)	131(57)	0.06
	APRI	0.11 (0.17)	0.07 (0.04)	**0.001**
		Early-onset preeclampsia	**Late-onset preeclampsia**	
First trimester				
	SIRI	1.51 (1.13)	1.49 (1.28)	0.414
	SII	877 (653)	772 (408)	0.334
	PLR	150 (69)	124 (50)	0.745
	APRI	0.06 (0.03)	0.05 (0.03)	0.179
At the time of diagnosis				
	SIRI	1.96 (1.02)	1.85 (1.02)	**0.046**
	SII	904 (897)	1110 (549)	0.097
	PLR	121 (70)	133 (44)	0.719
	APRI	0.09 (0.08)	0.06 (0.09)	0.312
Prior to delivery				
	SIRI	2.45 (2.59)	2.09 (2.04)	0.389
	SII	1008 (881)	994 (1321)	0.143
	PLR	120 (73)	130 (88)	0.594
	APRI	0.15 (0.3)	0.07 (0.11)	**<0.001**
		Severe preeclampsia	**Non-severe preeclampsia**	
First trimester				
	SIRI	1.47 (1.34)	1.63 (1.1)	0.685
	SII	859 (622)	772 (624)	0.685
	PLR	150 (64)	124 (73)	0.201
	APRI	0.06 (0.04)	0.05 (0.02)	0.369
At the time of diagnosis				
	SIRI	1.96 (1.4)	1.8 (1.7)	0.379
	SII	904 (704)	998 (952)	0.787
	PLR	123 (58)	123 (69)	0.720
	APRI	0.09 (0.08)	0.09 (0.11)	0.370
Prior to delivery				
	SIRI	2.9 (2.5)	2.8 (2.7)	0.461
	SII	994 (884)	971 (1645)	0.257
	PLR	123 (65)	133 (92)	**0.027**
	APRI	0.17 (0.44)	0.08 (0.11)	**<0.001**
		HELLP	**Non-HELLP**	
First trimester				
	SIRI	1.52 (2)	1.44 (1.06)	0.176
	SII	891 (575)	787 (545)	0.975
	PLR	127 (65)	133 (62)	0.532
	APRI	0.07 (0.05)	0.06 (0.03)	0.878
At the time of diagnosis				
	SIRI	1.8 (1.7)	1.96 (1.34)	0.381
	SII	878 (653)	955 (675)	0.717
	PLR	98.9 (62.7)	133 (64)	0.077
	APRI	0.12 (0.05)	0.08 (0.05)	0.152
Prior to delivery				
	SIRI	3.88 (4.2)	2.08 (1.55)	**0.024**
	SII	740 (1459)	1008 (675)	0.082
	PLR	82 (118)	130 (62)	**<0.001**
	APRI	1.28 (1.98)	0.08 (0.07)	**<0.001**

* All variables were presented as medians and interquartile ranges. SII, systemic immune inflammation index; SIRI, systemic inflammation response index; PLR, platelet-to-lymphocyte ratio; APRI, alanine aminotransferase-to-platelet ratio; HELLP, hemolysis, elevated liver enzymes and low platelets.

thrombosis and decreased placental blood flow as a result of spiral artery occlusion (3). However, the pathophysiology of preeclampsia is highly complex, and the main pathways behind this deadly pregnancy-specific syndrome have not been clarified yet.

When APRI, SIRI, PLR and SII parameters were calculated for the time of diagnosis, the PLR index was found to be significantly lower in the preeclamptic group at the time of diagnosis due to the presence of lymphocytosis. However, most of the patients had normal platelet counts and higher APRI values prior to delivery in the preeclampsia group, resulting from the higher AST levels rather than the platelet count. Although platelets have many functions in the immune response of the patients, findings from this study indicated that platelet counts did not differ over time between the groups. On the other hand, there are publications in the literature reporting altered maternal platelet levels in the first trimester for preeclampsia cases (10).

When literature was analyzed in a study published in 2008, the cytokine-dependent immune interaction between platelets and lymphocytes was called heterotypic cross-talk, and it was stated that this interaction has great importance in thrombosis, atherogenesis and inflammation (11).

In a study conducted by Yucel et al. with the participation of 82 severe-preeclamptic, 27 non-severe-preeclamptic and 110 healthy pregnant women, PLR was found to be significantly lower in the severe-preeclamptic group. However, this study was conducted with pregnant women hospitalized for delivery (12). In another study designed with 824 pregnant women hospitalized for delivery, PLR was found to be statistically significantly lower when the severe-preeclamptic group, non-severe preeclamptic group and control group were compared (13).

Although the PLR index was found to be lower in the preeclamptic group at the time of diagnosis compared to the control group in this study, it was not found to be effective in predicting severe preeclampsia. Since most of the studies in the literature were conducted at the time of delivery, the PLR was calculated at the time of delivery, and it was significantly lower in the severe preeclamptic group compared with the non-severe preeclamptic group. However, since this difference emerges at delivery, cell-based inflammatory indices may have limited predictive value in predicting and prognosing preeclampsia. Yet, changes observed prior to delivery may help clarify the immune-mediated mechanisms underlying preeclampsia.

When the studies investigating first-trimester PLR for prediction of preeclampsia in the literature were examined, Gezer et al. found that PLR was higher in the preeclamptic group in the first trimester

(14). However, Sisti et al. found no significant change in first-trimester PLR for prediction of HELLP in another study (15).

When first-trimester PLR was calculated, no significant difference was observed between the control and preeclamptic groups. The first trimester PLR was unable to predict severe pre-eclampsia. First-trimester PLR was higher in patients with early-onset pre-eclampsia but not statistically significant (p-value 0.06). In addition, PLR was insufficient to predict HELLP syndrome in our study.

SIRI, SII and APRI, have been investigated to determine the prediction of HELLP syndrome and pre-eclampsia in the first trimester. SIRI and SII were investigated at the time of delivery and in the first trimester in the study by Ipek et al. SIRI was found to be high at the time of delivery, but none of the indices have been successful in predicting HELLP syndrome in the first trimester (15). In another study by Seyhanli et al., first-trimester SIRI was found to be statistically significantly higher in preeclamptic patients, but no significant change was shown for SII (5). Li et al. reported that APRI was an important marker of progression to HELLP syndrome with a sensitivity of 90% and specificity of 97% in a study including pregnant women with gestational hypertension and HELLP syndrome (16). In another study, APRI was found to be significantly higher in severe preeclampsia compared to non-severe preeclampsia, gestational hypertension and the control group. In the same study, APRI values at 20 weeks of gestation were reported to be successful in predicting severe pre-eclampsia (17).

Therefore, we investigated these new markers, SIRI, SII and APRI, for prediction and severity of preeclampsia. APRI, SII and SIRI calculated at the time of diagnosis were not statistically significantly different between the preeclamptic group and the control group, between the early-onset preeclamptic group and the late-onset preeclamptic group and between the severe preeclamptic group and the non-severe preeclamptic group. There was also no statistically significant difference in the first-trimester indices of these patients. However, when analyzing the APRI values at the time of delivery, APRI was significantly higher in both the severe preeclampsia and the early-onset preeclampsia groups.

We found that APRI was statistically significantly higher only at the time of delivery. As expected, APRI was also significantly higher in the HELLP group at the time of delivery, but APRI values calculated at the time of diagnosis were insufficient to predict HELLP. These findings can be attributed to the relatively limited number of cases and the retrospective design of the study.

This research has some limitations. The restricted number of patients diagnosed with HELLP syndrome may have limited the statistical power for subgroup analysis and restricted the generalizability of the findings. Secondly, although ROC curve studies were performed to evaluate the discriminative capacity of inflammatory indices, the resulting AUC values were insufficient to demonstrate diagnostic efficacy. Consequently, the cutoff values obtained from these studies were not included in the results

Eventually, there are controversial findings in the literature regarding the utility of novel inflammatory indices in preeclampsia most probably due to the heterogeneity of the studies. While some researchers found promising findings for prediction and management of pregnant women with preeclampsia, others do not report significant benefits. It is important to note that preeclampsia is a complex and multifactorial condition, and it is not possible to just use a simple index to provide optimal health care for women. A management protocol that includes medical history, risk factors, previous obstetric experiences, clinical findings, and novel methods like inflammatory indices may be a guide for clinicians to achieve favorable perinatal outcomes.

CONCLUSIONS

The inflammatory indices evaluated in this study appear to have limited value in predicting preeclampsia and its prognosis. However, significant inflammatory changes seem to occur before delivery in the study population. This result suggests that a systemic inflammatory response may occur late and could indicate a risk of poor clinical outcomes. We suggest that inflammatory indices derived from accessible, cost-effective, and reproducible tests may support early diagnosis and prognosis, provided that further studies are conducted in larger populations.

Ethics Committee Approval: This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-23-4881), according to the Helsinki Declarations.

Authors' Contributions: AGB: Investigation, Methodology, Writing—original draft; AT: Formal Analysis, Writing—Review & Editing; EGY: Investigation, Methodology, Writing—Original Draft; AP: Investigation, Formal Analysis, Methodology; GO: Investigation, Formal Analysis, Methodology; ÖK: Formal Analysis, Writing—Review & Editing; DŞ: Writing—review & editing, Validation, Supervision

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Evaluation of the Neutrophil Percentage Albumin Ratio (NPAR) Index in Predicting the Severity of Hyperemesis Gravidarum

Hiperemezis Gravidarumun Şiddetini Tahmin Etmede Nötrofil Yüzdesi Albümin Oranı (NPAR) Endeksinin Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study is to investigate the effect of the neutrophil percentage to albumin ratio (NPAR) index in determining the severity of hyperemesis gravidarum in patients diagnosed with this condition.

Material and Methods: In a retrospective, single-center study, pregnant women diagnosed with HEG between January 2024 and November 2025 at the Perinatology Department of Ankara City Hospital were included. NPAR was calculated by dividing the neutrophil percentage by the albumin value. HEG severity was classified as mild, moderate, or severe using the modified PUQE-24 scoring system. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of data distribution. Group comparisons were performed using the Kruskal-Wallis test. ROC analysis was performed for NPAR to predict HEG severity; $p<0.05$ was considered significant.

Results: A total of 160 HEG patients were included in the study: mild n=80, moderate n=40, severe n=40. No differences were found between groups in BMI, gestational age, and other parameters; however, hospital stay, and PUQE-24 scores were significantly higher in the severe HEG group. Both the neutrophil percentage and NPAR were significantly higher in the severe HEG group ($p=0.01$ and $p=0.009$). In the ROC analysis, the best cutoff value for NPAR was found to be 1.77; sensitivity was 70%, specificity was 68%, and AUC was 0.675 ($p=0.005$).

Conclusion: NPAR showed a statistically significant correlation in predicting HEG severity and partially distinguished between mild and severe HEG; however, its limited performance, with an AUC of 0.675, indicates that NPAR alone is not sufficient for clinical decision-making. These findings suggest that NPAR may provide additional information when used with PUQE-24 and necessitate validation through prospective/multicenter studies.

Keywords: Hyperemesis gravidarum, neutrophil percentage albumin ratio, severity

ÖZ

Amaç: Bu çalışmadaki amacımız hiperemezis gravidarum tanılı hastalarda nötrofil yüzdesinin albümine oranı(NPAR) indeksinin hastalığın şiddetini belirlemede etkisini araştırmak.

Gereç ve Yöntemler: Retrospektif, tek merkezli bir çalışmada, Ankara Şehir Hastanesi Perinatoloji Bölümü'nde Ocak 2024 – Kasım 2025 döneminde HEG tanısı konulan gebeler dahil edildi. NPAR hesaplanırken neutrofil yüzdesi, albumin değerine bölünerek elde edildi. HEG şiddeti, modifiye PUQE-24 skorlama sistemiyle mild, moderate ve severe olarak sınıflandırıldı. Veri dağılımı normalliği için Kolmogorov-Smirnov ve Shapiro-Wilk testleri kullanıldı. Grup karşılaştırmaları Kruskal-Wallis testiyle yapıldı. HEG'nin şiddetini tahmin etmek için NPAR için ROC analizi yapıldı; $p<0,05$ anlamlı kabul edildi.

Bulgular: Toplam 160 HEG hastası çalışmaya alındı: hafif n=80, orta n=40, ağır n=40. BMI, gebelik süresi ve diğer bazı parametrelerde gruplar arasında fark saptanmadı; ancak ağır HEG grubunda hastanede kalış süresi ve PUQE-24 skorları anlamlı derecede yüksek bulundu. Hem neutrofil yüzdesi hem de NPAR, ağır HEG grubunda anlamlı olarak yüksekti ($p=0,01$ ve $p=0,009$). ROC analizinde NPAR için en iyi kesim değeri 1.77 olarak bulundu; sensivite %70, spesifiklik %68, AUC 0,675 ($p=0,005$).

Sonuç: NPAR, HEG şiddetinin tahmininde istatistiksel olarak anlamlı bir ilişki gösterdi ve hafif ile ciddi HEG arasındaki ayırımı kısmen sağladı; ancak AUC 0,675 gibi sınırlı bir performans olması NPAR'ın tek başına klinik karar için yeterli olmadığını göstermektedir. Bu bulgular, NPAR'ın PUQE-24 ile kullanıldığında ek bilgi sağlayabileceğini ve prospective/çok merkezli çalışmalarla doğrulamanın gerekliliğini düşündürmektedir.

Anahtar Kelimeler: Hiperemezis gravidarum, nötrofil yüzdesinin albümine oranı, şiddet

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INTRODUCTION

Nausea is a common condition in early pregnancy, and mild nausea can be considered a normal part of pregnancy physiology in the first and early second trimesters. However, these symptoms significantly affect the quality of life of both the pregnant person and their family, especially when they are persistent and/or severe.Severe symptoms can negatively affect daily functioning, lead to anxiety and depression, and in some patients, cause thoughts of terminating the pregnancy or avoiding future pregnancies (1-3).

The etiology of nausea and vomiting is not fully understood. Factors such as genetics, hormonal changes, abnormal gastrointestinal motility, and H. pylori are considered in the etiology (4).

Patients with severe nausea and vomiting (hyperemesis gravidarum) may present with orthostatic hypotension, laboratory abnormalities (e.g., electrolyte, thyroid, and liver abnormalities), and signs of hypovolemia. They usually require hospitalization for stabilization and initiation of pharmacotherapy (5).

Albumin has gained prominence in obstetric research due to its easy accessibility and potential prognostic value in pregnancy-related complications(5, 6) . These indices, which include albumin as an important component, provide insight into both the inflammatory and nutritional status of patients. While white blood cells provide additional information about the inflammatory process, albumin levels are an indicator of nutritional status (7).

It was hypothesized that an index created using albumin and white blood cells would be effective in determining the severity of hyperemesis gravidarum (HEG), given the deterioration of the mother's nutritional status and the immune-related nature of pregnancy associated with HEG. This formed the basis of our study.

The aim of this study is to evaluate the neutrophil percentage to albumin ratio (NPAR) index in determining the severity of HEG.

MATERIALS AND METHODS

Study Population

This study was retrospective, single-center, and conducted at a tertiary care hospital. Patients diagnosed with HEG and treated at the Perinatology Department of Ankara City Hospital between January 2024 and November 2025 were included in this study. Informed consent forms were obtained from all patients included in the study. Approval was obtained from the Ankara City Hospital Ethics Committee for this study (TABED-2-25-1629). The Helsinki Declaration guidelines were followed at every stage of the study.

For each patient included in the study, the following clinical and obstetric data were retrospectively recorded from the hospital database: age, gravida, parity, body mass index, gestational age at the onset of HEG, length of hospital stay, results of routine liver function tests performed at diagnosis, electrolyte levels, ketone levels in spot urine, thyroid function test results, hemoglobin, neutrophil percentage, and albumin, NPAR values, were retrospectively recorded from the hospital database.

NPAR was calculated by dividing the neutrophil percentage by the albumin value.

The diagnosis of HEG was made when severe vomiting, weight loss of more than 5%, and urinary ketonuria or maternal serum electrolyte imbalance were observed in the first weeks of pregnancy after other causes were excluded (8). The severity of HEG was assessed using the modified PUQE-24 system (9) based on anamnesis information (Table 1). Using the PUQE-24 scoring system, patients with HEG were divided into three groups: mild, moderate, and severe.

The study excluded patients with multiple pregnancies, hypertensive patients, diabetic patients, psychiatric patients, patients with a history of molar pregnancy, and those with missing or inaccessible data.

Statistical Analysis

In this study, the sample size was analyzed using G Power software (version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany). A 0.05

Table 1. Pregnancy-Unique Quantification of Emesis Scoring System

In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4–6 hours (4)	More than 6 hours (5)
In the last 24 hours, have you vomited or thrown up?	I did not throw up (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)
in the last 24 hours, how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

Mild = ≤6; Moderate = 7–12; Severe = 13–15.

Table 2. Clinicodemographic and obstetric data, length of hospital stay, and PUQE-24 scores of the patients with HEG

Variables	Mild HG N:80	Moderate HG N:40	Severe HG N:40	P-value
Age (year)	28(19-41)	27(20-43)	28(23-38)	0.413
Gravida	2.0(1.0-5.0)	2.0(1.0-8.0)	2.0(1.0-4.0)	0.983
Parity	0.0(0.0-4.0)	0.0(0.0-5.0)	0.0(0.0-2.0)	0.643
BMI (kg/m^2)	24(18-32)	23(20-30)	24(21-35)	0.756
Miscarriage	0.0(0.0-4.0)	0.0(0.0-2.0)	0.0(0.0-3.0)	0.212
Gestational week	11.0(6.0-20.0)	10.0(6.0-19.0)	9.0(4.0-15.0)	0.302
Length of hospital stay	2.0(1.0-3.0)	5.0(1.0-.5.0)	9.0(7.0-29)	**<0.001**
PUQE-24 score	3.0(1.0-5.0)	7.0(6.0-12.0)	15(12.0-15.0)	**<0.001**

HEG: hyperemesis gravidarum, PUQE: Pregnancy-Unique Quantification of Emesis
Descriptive analyses used median min-max for non-normally distributed variables. Statistically significant at p < 0.05

(two-tailed) p-value and 95% power with an 0.80 (large) effect size were determined for the sample size. The sample size was calculated as 100 patients in each group.The SPSS 22.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for data analysis. The Kolmogorov–Smirnov test and Shapiro–Wilk test were used to analyze the normality of the data distribution. The Kruskal-Wallis test was used to compare variables that did not follow a normal distribution. Descriptive analyses used median min-max for non-normally distributed variables. The "ROC" curve was used to determine the cut-off point of NPAR in predicting HEG severity. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 160 HEG patients were included in the study. Patients were divided into three groups based on the severity of HEG. There were 80 patients in the mild HG group, 40 in the moderate HG group, and 40 in the severe HEG group. Table 2 presents the patients clinical demographic and obstetric data, body mass index (BMI), gestational age at diagnosis, length of stay and PUQE-24 scores.

There was no significant difference in body mass index among the three groups in terms of gestational age at diagnosis of gravida, parity, miscarriage, and HEG (p>0.05) (Table 2). Hospitalization durations and PUQE-24 scores were statistically significantly higher in the severe HEG group (p<0.001, respectively).

Table 3 shows the comparison of laboratory blood results and NPAR values between mild, moderate, and severe HEG groups. In terms of laboratory values, ALT and AST values were found to be higher in the severe HEG group among the three groups (p=0.008; p<0.001, respectively). Neutrophil percentages and NPAR values were also found to be higher in severe HEG (P=0.01; 0.009, respectively). No difference was observed between the three groups in terms of glucose, creatinine, calcium, sodium, potassium, (Thyroxine) T4, TSH (Thyroid Stimulating Hormone), total albumin, and albumin levels (p>0.05). Urea levels were lower in the severe HEG group (p=0.021).

Spot urine ketone levels for the HEG groups are presented in Table 3. There was no significant difference between the three groups in terms of ketone levels measured in spot urine (p>0.05).

In the ROC analysis, the optimal cutoff value of NPAR for predicting severe HEG was determined to be 1.77 with 70% sensitivity and 68% specificity (area under the curve = 0.675; p=0.005) (Figure 1).

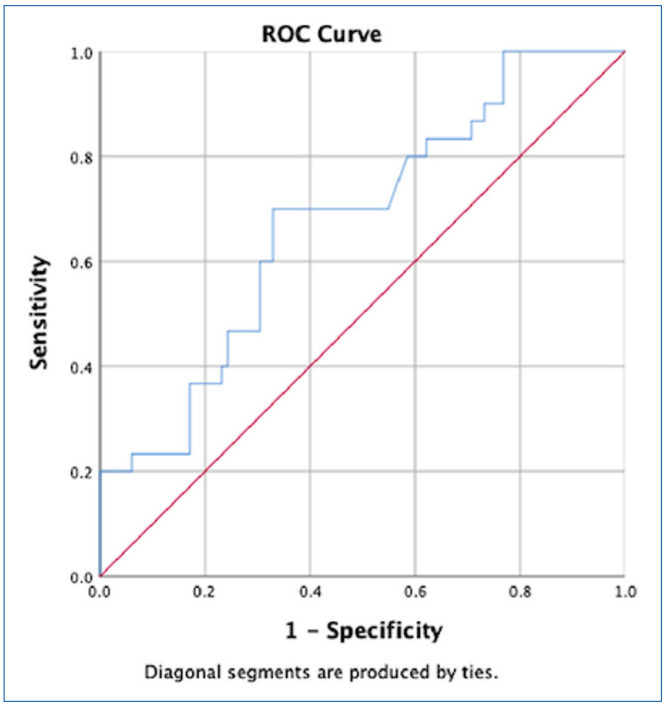

Figure 1. The ROC curve for the Neutrophil Percentage Albumin Ratio ratio to predict severe hyperemesis gravidarum

Table 3. Laboratory parameters and NPAR values of the patients with HEG

Variables	Mild HG N:80	Moderate HG N:40	Severe HG N:40	P-value
Glucose(mg/dl)	82(56-149)	86(68-116)	83(68-109)	0.772
ALT (IU/L)	20(8-186)	35(10-135)	40(9-68)	**0.008**
AST (IU/L)	15(4-71)	16(6-64)	22(10-81)	**<0.001**
Creatinine (mg/dL)	0.50(0.34-0.75)	0.53(0.15-0.71)	0.51(0.38-0.64)	0.331
Calsium(mEq/L)	9.4(8.4-10.1)	9.1(8.9-9.3)	9.2(8.8-9.7)	0.298
Urea(mg/dl)	17(10-34)	16(9-21)	15(9-21)	**0.021**
Sodium (mEq/L)				0.357
Chlorine(mEq/L)	105(102-110)	103(103-107)	103(101-105)	0.181
Potassium (mEq/L)	3.8(3.4-4.1)	3.75(3.4-4.1)	4.1(4.0-4.2)	0.703
T4 (ng/dl)	1.19(0.88-3.0)	1.64(1.29-3.35)	1.24(0.95-3.19)	0.105
TSH (mU/ml)	0.7(0.00-2.51)	0.02(0.00-0.21)	0.65(0.00-1.72)	0.752
Hemoglobin	12.9(10.3-14.8)	12.5(11.2-15.5)	13.4(10.5-15.5)	**0.028**
WBC	8.97(3.14-14.9)	9.73(6.53-15.9)	8.19(6.41-17.0)	0.764
Neutrophil persentage	71.8(56.5-92.8)	76.4(65.3-88.2)	80.0(68.7-81.6)	**0.001**
Total protein	67(54-81)	66(59-73)	66(55-82)	0.452
Albumin (g/dL)	43(32-51)	38(36-45)	43(32-53)	0.666
NPAR	1.72(1.37-2.29)	1.78(1.56-2.48)	1.81(1.46-2.27)	**0.009**
Ketone	3(0-4)	3(0-4)	4(4-4)	**0.018**

NPAR:Neutrophil persentage albümin ratio,HG: hyperemesis gravidarum, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TSH: thyroid-stimulating hormone
Descriptive analyses used median min-max for non-normally distributed variables. Statistically significant at $p < 0.05$

DISCUSSION

In this study, we evaluated the effect of NPAR in predicting disease severity in HEG patients. We found that NPAR had 70% sensitivity and 67% specificity in predicting the severity of HG.

Nausea, with or without vomiting, occurs in up to 90% of pregnancies (9).

Nausea begins in the 5th to 6th week of pregnancy, peaks around the 9th week, and usually subsides between the 16th and 20th weeks. Sixty percent of patients are asymptomatic six weeks after the onset of nausea (10). However, symptoms persist into the third trimester in 15 to 20 percent of patients and until delivery in 5 percent (11). Although mild pregnancy-related nausea and vomiting are often referred to as “morning sickness,” symptoms can occur at any time of day, may only occur in the evenings, and typically persist throughout the day (80%) (12).

Hyperemesis gravidarum is a term used to describe the severe end of the symptom spectrum (13). Severe symptoms can negatively impact daily functioning, leading to anxiety and depression. In some cases, it may even cause patients to consider terminating the pregnancy or avoiding future pregnancies (14).

The indices used to determine the severity of hyperemesis in hyperemesis gravidarum are the Motherisk-PUQE Scoring Index and the Rhodes Index. The Motherisk-PUQE Scoring Index is specifically designed for pregnant individuals to assess symptoms within the 12 hours prior to clinical evaluation and has been used primarily in research studies (15). The modified PUQE score is designed to assess symptoms throughout the entire first trimester (16). We also used the modified PUQE scoring index in our study. The scoring system includes the number of hours the individual felt nauseous, the number of times they vomited, and the number of times they experienced dry retching in a day. A high score should prompt immediate evaluation for hypovolemia and serum electrolyte abnormalities. As the severity of HEG increases, maternal and perinatal outcomes become more complicated(8) . Therefore, predicting the severity of the disease and implementing personalized treatment approaches for patients is crucial for improving maternal and perinatal outcomes.

In a meta-analysis compiling studies predicting HEG severity, inconsistent relationships with HEG were found in studies on human chorionic gonadotropin, thyroid hormones, leptin, estradiol, progesterone, and white blood cell count; lymphocytes were found to be higher in women with HEG.In our study, although the white blood cell count was the same in all three groups, the neutrophil percentage was found to be higher in the HEG group (17). Another study found that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were higher in the HEG group (18). The usefulness of these methods remains controversial, and their relative superiority is unclear.

Albumin constitutes more than half of total serum proteins. It plays a role in various functions, including osmotic regulation, antioxidant

and anti-inflammatory effects, nutrient and drug transport, and acid-base balance regulation (19). Neutrophils are also mediators involved in the inflammatory process. The combination of these two components may be used to predict HEG severity, given that vomiting leads to maternal malnutrition and pregnancy is associated with an immune response.

As this study was retrospective, single-center, and conducted in a tertiary hospital, the generalizability of the findings is limited. Due to tertiary capacity, the focus was on a patient group with complex cases, and it may reflect the performance of NPAR at a different level in different healthcare system settings. Due to the limited sample size, the predictive power may be limited and may not fully reflect the effect of rare subgroups. The true clinical diversity may not be fully represented due to cases excluded from the study (multiple pregnancies, molar pregnancies, hypertension, diabetes mellitus, psychiatric disorders, those with major fetal anomalies, and those with missing/lost data).

There are some limitations in terms of diagnosis and classification. HEG severity was classified using a modified scoring system based on PUQE-24; this approach is subject to clinically subjective biases and may lead to inconsistencies when applied by different clinicians. Furthermore, neutrophil percentage and albumin values in NPAR calculation were obtained at a single time point; dynamic changes (course, treatment effects) could not be considered.

On the other hand, examining the potential role of NPAR, which reflects inflammation and nutritional status, for early prediction of HEG severity offers a valuable perspective for clinical practice. Modifying PUQE-24 to classify HEG severity and integrating biochemical and hematological parameters could provide a broad knowledge base for clinical decisions.

The fact that the NPAR value consists of simple and widely accessible laboratory parameters, and that NPAR can rapidly reflect inflammation and nutritional status, makes it a potential decision support tool.In the severe HG group, the significant elevation of the neutrophil percentage and certain biochemical differences with NPAR are noteworthy, supporting the notion of a strengthened relationship between inflammation and nutritional status.

This study has demonstrated that NPAR shows high sensitivity in predicting disease severity in HEG patients. When evaluated together with the PUQE-24 score, NPAR may be useful as a clinical decision support tool; however, it is not sufficient for decision-making on its own.

Future studies should be conducted with prospective, multicenter designs and the development of multivariate models: The integration of inflammation and nutrition indicators such as NLR, PLR, CRP, IL-6, and total protein/albumin ratios in addition to NPAR will more clearly demonstrate the prognostic value and clinical benefit of NPAR.

Ethics Committee Approval: The study received ethical approval from the Ethics Committee of Ankara City Hospital (TABED-2-25-1629). All procedures were performed according to the Declaration of Helsinki.

Availability of Data and Materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

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Author Contribution: BBÖ: Design the method to achieve results, Data collecting and processing, Literature scan, Article writing; DS: Article writing, Critical examination, Critical examination

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The Association Between APRI, FIB-4 and FIB-5 Scores, Hiperemesis Gravidarum and Disease Severity

APRI, FIB-4 ve FIB-5 Skorları ile Hiperemezis Gravidarum ve Hastalık Şiddeti Arasındaki İlişki

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ABSTRACT

Aim: The aim of this study is to determine the association between hyperemesis gravidarum and the non-invasive liver fibrosis indices APRI, FIB-4, and FIB-5, in order to evaluate whether these indices could be used as predictive markers for the presence and severity of the disease.

Materials and Methods: This cross-sectional retrospective study was conducted on 100 pregnant women diagnosed with HG, and 100 gestational age- and age-matched healthy pregnant women, at a tertiary hospital between December 2022 and December 2024. Demographic data, laboratory parameters, and PUQE scores were collected from the hospital database and APRI, FIB-4, and FIB-5 scores were calculated using standard formulas. Comparisons were made between the two groups, and any correlations between disease severity and these indices were determined. Logistic regression and ROC analysis were performed to identify the predictive value of these scores.

Results: Mean APRI and FIB-4 scores were significantly higher in the HG group compared to controls, while FIB-5 scores were significantly lower ($p<0.001$). Increased disease severity correlated with rising APRI and FIB-4 and decreasing FIB-5 scores. Logistic regression revealed APRI and FIB-4 as independent predictors of both disease presence and severity (OR for APRI = 19.267 and 5.945; OR for FIB-4 = 3.218 and 4.502, respectively). ROC analysis identified optimal cut-off values for APRI (≥0.25) and FIB-4 (≥0.64) with high sensitivity and specificity in identifying HG.

Conclusion: APRI and FIB-4 are significantly elevated in patients with HG and strongly correlate with disease severity. These simple, cost-effective, and non-invasive indices have the potential of being valuable tools in the early identification and risk stratification of HG, as well as determining the severity of the disease.

Keywords: Hyperemesis gravidarum; APRI; FIB-4; FIB-5; liver fibrosis; non-invasive biomarker

ÖZ

Amaç: Bu çalışmanın amacı, hiperemezis gravidarum (HG) ile noninvaziv karaciğer fibrozis belirteçleri olan APRI, FIB-4 ve FIB-5 arasındaki ilişkinin belirlenmesi ve bu indekslerin hastalığın varlığı ve şiddetinin öngörücü belirteçleri olarak kullanılıp kullanılamayacağının değerlendirilmesidir.

Gereç ve Yöntemler: Bu kesitsel retrospektif çalışma, Aralık 2022–Aralık 2024 arasında üçüncü basamak bir hastanede HG tanısı alan 100 gebe ile gebelik haftası ve yaş açısından eşleştirilmiş 100 sağlıklı gebe üzerinde yürütüldü. Demografik veriler, laboratuvar parametreleri ve PUQE skorları hastane veri tabanından elde edildi; APRI, FIB-4 ve FIB-5 skorları standart formüllerle hesaplandı. İki grup arasında karşılaştırmalar yapıldı ve hastalık şiddeti ile bu indeksler arasındaki korelasyonlar değerlendirildi. Bu skorların öngörü değerini belirlemek amacıyla lojistik regresyon ve ROC analizi uygulandı.

Bulgular: HG grubunda ortalama APRI ve FIB-4 skorları kontrol grubuna kıyasla anlamlı derecede yüksek, FIB-5 skorları ise anlamlı derecede düşüktü ($p<0,001$). Hastalık şiddetindeki artış, APRI ve FIB-4'te yükseliş ve FIB-5'te düşüş ile koreleydi. Lojistik regresyon analizi, APRI ve FIB-4'ün hem hastalık varlığının hem de şiddetinin bağımsız belirleyicileri olduğunu gösterdi (APRI için OR = 19,267 ve 5,945; FIB-4 için OR = 3,218 ve 4,502; sırasıyla). ROC analizi, HG'yi saptamada yüksek duyarlılık ve özgüllükle APRI için ≥0,25 ve FIB-4 için ≥0,64 en uygun kesim değerlerini belirledi.

Sonuç: HG'li hastalarda APRI ve FIB-4 anlamlı olarak yüksektir ve hastalık şiddeti ile güçlü biçimde ilişkilidir. Bu basit, maliyet etkin ve noninvaziv indeksler, HG'nin erken tanımlanması ve risk sınıflamasında, ayrıca hastalık şiddetinin belirlenmesinde değerli araçlar olma potansiyeline sahiptir.

Anahtar Kelimeler: Hiperemezis gravidarum, APRI, FIB-4, FIB-5, karaciğer fibrozisi, invaziv olmayan biomarker

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INTRODUCTION

Hyperemesis gravidarum is the most severe form of nausea and vomiting during pregnancy and is one of the most frequent causes of hospitalization, especially in the first trimester. The condition is typified by uncontrollable vomiting during pregnancy, characterized by dehydration leading to electrolyte and acid-base imbalance, nutritional deficiencies, and weight loss that exceeds 5% of pre-pregnancy body weight (1). Severe symptoms negatively affect the patient's day-to-day life, causing anxiety and depression, but also seriously reducing the patient's quality of life. Suffering from hyperemesis gravidarum may cause some patients to consider terminating the pregnancy, or perhaps resolving not to become pregnant again (2). The etiology of important pregnancy complication, which is an important factor in pregnancy morbidity, is known to be multifactorial and has not been clearly elucidated.

Although it has been estabished in the literature for many years that endocrine, biological, psychosocial and socioeconomic factors play a role in etiology, hyperemesis gravidarum is considered to be one of the pregnancy-specific liver diseases, along with preeclampsia, acute fatty liver of pregnancy and intrahepatic cholestasis of pregnancy (3). Liver complications are observed in approximately 50-60% of patients, and may include not only mild elevations in serum aminotransferase levels, but also serious elevations up to 1000 u/L and a condition involving moderate hyperbilirubinemia and jaundice (4). Although rare, cases of serious complications with hyperemesis gravidarum, such as severe hyperammonemia and atypical acute liver failure, have been reported in the literature (5). The etiology of liver injury due to HG remains unclear, but multiple factors including dehydration, starvation, human chorionic gonadotropin, and placental-derived cytokines, such as tumor necrosis factor-alpha, may be involved in hepatocellular injury. Early diagnosis and treatment of HG is therefore very important as, while it does not cause serious problems for the fetus, it can cause serious complications for the mother. Such complications can be significantly reduced with early diagnosis (6).

Aspartate-aminotransferase (AST)-to-platelet ratio index (APRI), Fibrosis-4 Index (FIB-4) and Fibrosis-5 Index (FIB-5) are non-invasive tests, which can be calculated using simple blood tests, and are considered early markers of liver damage and dysfunction. They have a well-documented association with clinical outcome and are used to evaluate the risk of liver fibrosis and provide important alternatives to invasive liver biopsies (7).

The aim of this study is to determine the association between APRI, FIB-4 and FIB-5 scores and the severity of hyperemesis gravidarum.

Key Messages

What is already known on this topic: Hyperemesis gravidarum is a severe pregnancy complication known to cause liver function abnormalities in over half of the women affected. While liver fibrosis indices, such as APRI, FIB-4, and FIB-5 have been studied in other pregnancy-related hepatic disorders, their role in HG remains underexplored.

What this study adds: This study is the first to comprehensively evaluate the relationship between non-invasive liver fibrosis markers—APRI, FIB-4, and FIB-5—and both the presence and clinical severity of hyperemesis gravidarum (HG). It demonstrates that higher APRI and FIB-4 scores, as well as lower FIB-5 scores, are significantly associated with increased severity of HG, suggesting hepatic involvement even in early gestation. The findings support the use of APRI and FIB-4 as accessible, cost-effective tools for identifying patients at higher risk of severe HG, potentially improving early clinical decision-making and individualized management strategies.

How this study might affect research, practice, or policy: By establishing APRI and FIB-4 as being reliable and non-invasive predictors of HG, this study suggests their use in routine obstetric assessment protocols. It is also hoped that this study may encourage future research into liver-related pathophysiology of HG, and support early identification strategies to reduce maternal morbidity.

MATERIAL AND METHODS

This cross-sectional retrospective study was conducted between December 2022 and December 2024 in the antenatal clinic of a tertiary care hospital in Ankara, Turkey. Patients who had a singleton live pregnancy of ≤ 12 weeks, and who were hospitalized due to being diagnosed with hyperemesis gravidarum, were included in the study group (n=100). The singleton live pregnancy healthy control group (n=100), without hyperemesis, who were of a similar age and week of pregnancy, had come to the outpatient clinic for antepartum follow up. After approval from the Ministry of Health of the Republic of Türkiye, Sağlık Bilimleri University Ankara Atatürk Sanatoryum Training and Research Hospital Approval and Ethics committee (Approval No: 12.02.2025/219), data including age, demographic characteristics, gestational age (according to ultrasound performed at the hospitalization), laboratory values (AST, ALT, ALP, platelet ve albumin) and PUQE scores (A PUQE test is routinely performed at the hospitalization of each patient in our clinic to determine the severity of HG) were recorded on the computerized system of the hospital. The groups were compared in terms of APRI, FIB-4 and FIB-5 scores, and the study group was evaluated separately in terms of the relationship between the severity of the disease and APRI, FIB-4 and FIB-5 scores.

The exclusion criteria were as follows: an age of <20 and >40 years, >12 weeks pregnancy, additional liver pathology, systemic infections (urinary tract etc.), multiple pregnancies and patients whose data cannot be accessed from the system.

The Puqe test is a 3-question test that questions the severity of nausea and vomiting in the last 12 hours. The test is scored between 3-15 according to the patients' answers, and those with 4-6 points are considered as mild, those with 7-12 points are as moderate, and those with 13 and above are classed as being severe.

APRI is Aspartate-aminotransferase (AST)-to-platelet ratio index. Its formulation is:

AST X Upper limit of AST/ Platelet X 100.

FIB-4 (Fibrosis-4) is the index for liver fibrosis and is derived from a formula that includes age, AST, ALT, and platelet count. Its formulation is: Age × AST / Platelet × ALT.

FIB-5 (Fibrosis-5) is the index for liver fibrosis and is calculated based on measurements of blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, platelet count, and albumin. Its formulation is: [albumin × 0.3 + platelet count × 0.05]–[ALP × 0.014 + AST/ALT ratio × 6 + 14].

RESULTS

No differences were found between the groups in socio-demographic characteristics, as shown in Table 1 (p>0.05), such as age, BMI, educational level, average monthly income, and gestational history. The PUQE test results showed that 44.0% (n=44) in the study group had mild, 35.0% (n=35) had moderate, and 21.0% (n=21) had severe symptoms. A significant difference was found between the mean urine ketone levels of the mild, moderate and severe groups, and ketone levels increased in parallel with the severity of nausea. The mean ketone values of the mild, moderate and severe study groups were 1.25±0.49; 2.00±0.59; 3.23±0.53 (p<0.001) respectively.

The mean APRI (0.47±0.12; 0.19±0.07) and FIB-4 (0.91±0.24; 0.50±0.16) scores were significantly higher, while the mean FIB-5 (33.88±3.54; 35.83±3.63) scores were significantly lower, in the study group, as shown in Table 2 (p<0.001).

Table 1. Comparison of socio-demographic and maternity characteristics of the groups

Variable	Study group		Control group		Statistical analysis* Probability
	$\bar{X}$ ± S.S	Median [IQR]	$\bar{X}$ ± S.S	Median [IQR]	
Age (years)	27.17±5.01	27.0 [7.0]	28.53±5.47	28.0 [8.8]	Z=-1.704 p=0.088
Week of gestation	9.72±2.02	9.9 [3.5]	9.06±1.78	8.9 [2.9]	Z=-1.182 p=0.237
Gravida	2.30±1.39	2.0 [2.0]	2.40±1.59	2.0 [2.0]	Z=-0.259 p=0.796
Parity	0.89±0.92	1.0 [1.0]	1.08±1.13	1.0 [2.0]	Z=-0.975 p=0.330
Abortion	0.39±0.98	0.0 [0.0]	0.32±0.91	0.0 [0.0]	Z=-0.436 p=0.663
BMI (kg/m2)	25.38±3.89	25.0 [7.0]	25.43±3.85	25.0 [5.0]	Z=-0.013 p=0.989
	n	**%**	**N**	**%**	
Employment status					
Yes	35	35.0	40	40.0	$\chi^{2=0.533 p=0.465}$
No	65	65.0	60	60.0	
Level of education					
Primary/secondary school	27	27.0	19	19.0	$\chi^{2=2,800}$ p=0.247
High school	59	59.0	60	60.0	
University	14	14.0	21	21.0	
Spouse education level					
Primary/secondary school	9	9.0	8	8.0	$\chi^{2=2.170 p=0.338}$
High school	77	77.0	70	70.0	
University	14	14.0	22	22.0	
Average monthly income					
Below minimum wage	16	16.0	13	13.0	$\chi^{2=0.510 p=0.775}$
Minimum wage	63	63.0	63	63.0	
Above minimum wage	21	21.0	24	24.0	

*"Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in data that do not have a normal distribution. "Pearson-χ2" cross-tabulations were used to examine the relationships of two qualitative variables.

Table 2. Comparison of APRI, FIB-4, FIB-5 scores of the groups

Variable	Study group		Control group		Statistical analysis* Probability
	$\bar{X}$ ± S.S	Median [IQR]	$\bar{X}$ ± S.S	Median [IQR]	
APRI	0.47±0.12	0.5 [0.1]	0.19±0.07	0.2 [0.1]	Z=-11.981 **p<0.001**
FIB-4	0.91±0.24	0.9 [0.3]	0.50±0.16	0.5 [0.2]	Z=-10.614 **p<0.001**
FIB-5	33.88±3.54	33.5 [4.8]	35.83±3.63	35.9 [5.6]	Z=3.817 **p<0.001**

*In the normally distributed data, "Independent Sample-t" test (t-table value) statistics were used to compare the measurement values of the two independent groups. "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data without normal distribution.

Table 3. Comparison of APRI, FIB-4, FIB-5 scores and the severity of hyperemesis in the study group.

Variable	Mild (n=44) (1)		Moderate (n=35) (2)		Severe (n=21) (3)		Statistical analysis* Probability
	$\bar{X}$ ± S.S	Median [IQR]	$\bar{X}$ ± S.S	Median [IQR]	$\bar{X}$ ± S.S	Median [IQR]	
APRI	0.41±0.09	0.4 [0.1]	0.47±0.08	0.5 [0.1]	0.60±0.11	0.6 [0.2]	$\chi^{2=37,393}$ **p<0.001 [1-2.3] [2-3]**
FIB-4	0.74±0.14	0.7 [0.6]	0.91±0.13	0.9 [0.1]	1.26±0.21	1.3 [0.3]	F=78.805 **p<0.001 [1-2.3] [2-3]**
FIB-5	34.61±3.18	35.4 [4.6]	32.94±3.25	32.5 [4.5]	30.88±4.46	30.5 [7.1]	F=8.501 **p<0.001 [1-2.3] [2-3]**
Ketones in urine	1.25±0.49	1.0 [0.0]	2.00±0.59	2.0 [0.0]	3.23±0.53	3.0 [1.0]	$\chi^{2=63,666}$ **p<0.001 [1-2.3] [2-3]**

*In the normally distributed data, "ANOVA" test (F-table value) statistics were used to compare the measurement values of three or more independent groups. "Kruskal-Wallis H" test (χ 2-tabular value) statistics were used to compare the measurement values of three or more independent groups in data that did not have normal distribution.

A statistically significant difference was found in mean APRI, FIB-4 and FIB-5 scores according to PUQE categories in the study group (p<0.001). It was detected that as the mean APRI and FIB 4 scores, and the severity of nausea and vomiting increased, the mean FIB 5 scores decreased (p<0.001) (Table 3).

As a result of logistic regression analysis to determine the factors affecting the disease risk status; APRI, FIB-4 and FIB-5 scores were found to be important parameters affecting disease status (p<0.05). When the APRI and FIB-4 values increases by 0.1 units, the risk of disease increases by 19.267 and 3.218 respectively (OR=19.267; OR=3.218) and when FIB-5 value increases by 0.1 units, the risk of disease will decrease by 14.1% (OR=0.859).

As a result of logistic regression analysis performed to determine the factors affecting the severity of PUQE in patients; it was determined that APRI and FIB-4 values were important parameters affecting the severity of hyperemesis gravidarum (p<0.05). When the APRI value increases by 0.1 units, the risk of severe PUQE increases by 5.945-fold (OR=5.945), and when the FIB-4 value increases by 0.1 units, the risk of severe PUQE increases by 4.502 (OR=4.502).

The APRI cut-off value to be used to distinguish patients was found to be 0.25≥, with 98.0% sensitivity and 87.0% specificity (AUC=0.979; p<0.001). The FIB-4 cut-off value to be used to distinguish patients was found to be 0.64≥, with 90.0% sensitivity and 83.0% specificity (AUC=0.934; p<0.001). The FIB-5 cut-off value to be used to distinguish patients was 35.6≤, with 71.0% sensitivity and 54.0% specificity (AUC=0.656; p<0.001) (Figure 1).

Statistical Analysis

All data was analyzed using PASW statistics version 27.0 software (SPSS Inc, Chicago, IL). Results are presented as mean SD and n (%)."Independent Samples t-test" (t-table values) were used in the comparison of two dependent groups for data which had a normal distribution. The Mann-Whitney-U test was used for the comparison of two independent groups with non-normally distributed data. The "Pearson-χ^2" cross-tabulation test was used to examine the relationships between two categorical variables. "Binary logistic regression" was used to examine the factors affecting disease status and severe PUQE condition. "ROC" curves were employed

Table 4. Logistic Regression model based on disease risk and the severity of hyperemesis in the study group

Variable	B	S.H.	Wald	Sd	P	OR	95% Confidence Interval (OR)	
							Under	Top
APRI	2.958	0.441	45.070	1	**<0.001**	19.267	8.123	35.700
FIB-4	1.169	0.164	50.679	1	**<0.001**	3.218	2.333	4.439
FIB-5	-0.151	0.042	13.040	1	**<0.001**	0.859	0.792	0.933
Constant	5.274	1.466	12.945	1	**<0.001**	19.520		
CCR=85.5% $\chi2_{(8)}$=0.592; p=0.964								
Variable	**B**	**S.H.**	**Wald**	**Sd**	**P**	**OR**	**95% Confidence Interval (OR)**	
							Under	**Top**
APRI	1.782	0.376	22.442	1	**<0.001**	5.945	2.843	12.428
FIB-4	1.504	0.335	20.111	1	**<0.001**	4.502	2.332	8.688
Constant	-16.182	3.608	20.117	1	**<0.001**	0.001		
CCR=73.4% $\chi2_{(8)}$=4.173; p=0.841								

Table 5. ROC curve for APRI, FIB-4 and FIB-5 levels by disease status

Variable	Area	Standard Error	Probability	AUC 95% G.A.		Cut-off
				Under	Top	
APRI	0.979	0.009	**<0.001**	0.963	0.996	≥0.25
FIB-4	0.934	0.016	**<0.001**	0.903	0.966	≥0.64
FIB-5	0.656	0.038	**<0.001**	0.581	0.732	≤35.6

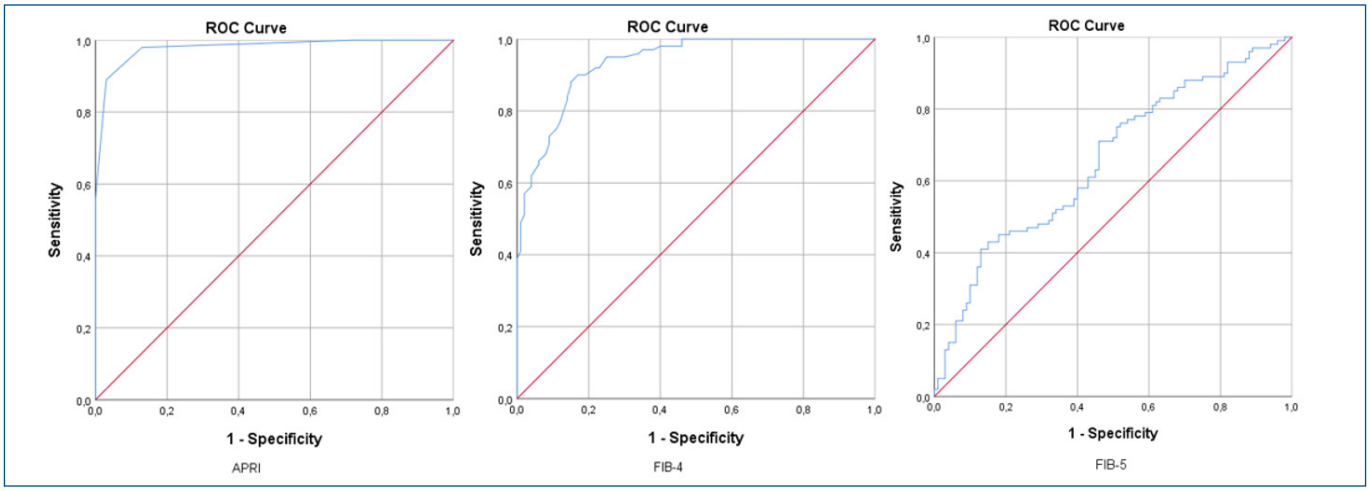

Figure 1. ROC curve for APRI, FIB-4 and FIB-5 levels by disease status

to determine the cut-off values of APRI, FIB-4, and FIB% scores in distinguishing disease status. P-values of <0.05 were considered significant.

DISCUSSION

Hyperemesis gravidarum is the most severe form of nausea and vomiting during pregnancy. The condition reduces the quality of life and often requires long-term hospitalization, making it a significant health problem with physiological, emotional, social and economic consequences for pregnant women and their families. Despite its importance, the multifactoral etiology of HG has not yet been clearly elucidated. This study, which was conducted to investigate the association between the markers known as early indicators of liver fibrosis, APRI, FIB-4 and FIB-5 and hyperemesis gravidarum and disease severity, found that the mean APRI and FIB-4 scores were significantly higher in the study group, while the mean FIB-5 scores were significantly lower. It was also detected that as the mean APRI and FIB 4 scores and the severity of nausea and vomiting increased, the mean FIB 5 scores decreased. As a result of logistic regression analysis, APRI, FIB-4 and FIB-5 scores were found to be important parameters that both affected disease status and the severity of hyperemesis gravidarum.

Although the studies on the relationship between HG and the early stage markers of fibrosis in the liver, APRİ, FIB-4 and FIB-5, have been extensively studied in recent years, there are other pregnancy conditions, such as preeclampsia and HELLP, which are considered, along with HG, to be pregnancy-specific liver diseases. In their study, Şaşmaz et al. (2020) investigate the role of APRI score in the diagnosis of HELLP syndrome, and concluded that APRI was a better predictor than AST score in predicting HELLP. The study found that when the cut-off value for the APRI levels were determined as 0.339, the sensitivity was 82.6%, and specificity 87.6% (8). In their study, Zhaoqi et al (2024), determined the markers that can be used to predict the progression of gestational hypertension to preeclampsia when complicated by HELLP syndrome, and Li et al concluded that APRI is one marker that can be used (9). In our study, which was conducted with hyperemesis gravidarum, which is among the diseases which affect the liver during pregnancy, although not as much as preeclampsi, mean APRI scores were found to be significantly higher in the hyperemesis group, which is consistent with these findings. Albayrak and Aslan (2025) also investigated the role of FIB-4 and FIB-5 in predicting preeclampsia in their study, and found that the FIB-4 index was significantly higher and the FIB-5 index values were lower in preeclampsia patients, compared to controls. They concluded that FIB-4 exhibited a better diagnostic performance with higher sensitivity and specificity (10). Similar to the findings of our study, FIB-4 scores were significantly higher, and the mean FIB-5 scores significantly lower, in the hyperemesis group. In their study, Cemortan et al. investigated the role of APRI and FIB-4 indices in intrahepatic cholestasis of pregnancy, another disease in which the liver is affected during pregnancy, and concluded that while both indices are reliable indicators of intrahepatic cholestasis, the APRI score was found to be more specific. Additionally, they found that these indices were promising markers in predicting complications such as meconium-stained amniotic fluid, premature birth, and increased cesarean section rates in pregnant women with intrahepatic cholestasis (11).

Although the relationship between APRI, FIB-4 and FIB-5 and HG has not yet been sufficiently studied in the literature, the relationship between liver and HG has been widely covered for many years. Approximately 50-60% of patients with HG are at risk of liver involvement. In their research, Lee and Brady stated that the most common symptom is mild serum aminotransferase elevation, but serious elevations at levels of 400-1000 U/L can also be seen, and mild hyperbilirubinemia and jaundice, electrolyte disturbances and acid-base imbalances can also occur (3). Worede et al investigated the prevalence of biochemical abnormalities in this population in order to reduce maternal/fetal morbidity and mortality due to electrolyte imbalances and liver test abnormalities in pregnant women with hyperemesis gravidarum, as well as to better understand the nature of the disease (12). The study concluded that HG is a cause of significant elevation in liver enzymes, as well as considerable disturbances in electrolyte levels, and that the severity of HG is an important factor affecting abnormal liver function tests. Similar to the findings of that study, we determined the presence of a significant correlation between diseases severity and APRI, FIB-4, FIB-5 scores. We also detected that as the severity of nausea and vomiting increased, the mean APRI and FIB 4 scores increased, while the mean FIB 5 scores decreased. Garcio-Ramero et al. (2019), in their review investigated the medical aspects of liver diseases in pregnancy and the fetal and maternal effects, stated that although HG is not considered a true liver disease, it is associated with abnormal liver function tests in about half of the patients (13). Although the relationship between HG and early liver fibrosis indices is limited in the literature, logistic regression analysis in our study showed that the increase in APRI, FIB-4 scores and the decrease in FIB-5 scores are important parameters affecting the risk and severity of HG.

The cross-sectional nature of the research, the small number of participants, being conducted with a homogeneous group, and retrospective design, can all be considered limitations of the study. This study would be therefore be strengthened with a longitudinal design and a larger population.

In conclusion, as HG is the most severe form of nausea and vomiting during pregnancy, which is a significant health problem during this period, early recognition of patients at risk is important in order to apply correct management in reducing the decline in quality of life. Our findings suggest that early liver indices, which are cheap and easy parameters to consider, may be important parameters in predicting patients with HG who are at risk, although it is important to support such a finding with comprehensive, multicenter, prospective and randomized controlled studies.

Ethics approval and consent to participate: This study was approved by the Ministry of Health of the Republic of Türkiye, Sağlık Bilimleri University Ankara Atatürk Sanatoryum Training and Research Hospital Approval and Ethics committee, under approval number (Approval No: 12.02.2025/219). Written informed consent was obtained from all participants.

Consent for publication : Written informed consent for publication of the data included in this study was obtained from all participants.

Competing interests: The authors declare that they have no competing interests.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Investigating the Impact of Birth Method on the Development of Postpartum Depression

Doğum Yönteminin Postpartum Depresyon Gelişimi Üzerine Etkisinin Araştırılması

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ABSTRACT

Aim: Postpartum depression (PPD) is a significant depressive disorder occurring after childbirth. Although traditionally defined as major depressive disorder manifesting within one month postpartum, PPD can also arise during pregnancy or beyond the first postpartum month. Affecting approximately 10–15% of women in developed countries, PPD poses serious consequences for both mother and child. This study aims to evaluate whether the mode of delivery is a risk factor for PPD, determine postpartum depression rates, and increase awareness of this condition.

Material and Methods: This prospective cohort study was conducted at the Department of Obstetrics and Gynecology of our hospital between March and June 2025. Women undergoing cesarean or vaginal deliveries who presented for postpartum check-ups between 7 and 14 days after delivery were screened for PPD using the Patient Health Questionnaire-9 (PHQ-9). Clinico-demographic characteristics, PHQ-9 scores, and PPD rates were compared between delivery groups.

Results: Among 289 participants, 67 (23.1%) screened positive for PPD. The median PHQ-9 score was 6.5 in the vaginal delivery group and 7.5 in the cesarean section group. PPD prevalence was 25.4% in the vaginal delivery group and 19.8% in the cesarean section group. These differences were not statistically significant (p=0.628 and p=0.268, respectively).

Conclusion: The prevalence of PPD in our population aligns with or slightly exceeds rates reported in the literature. Cesarean delivery does not appear to confer additional risk for PPD. Given the profound impact of maternal mental health on the mother, infant, and family, healthcare providers, including obstetricians, pediatricians, family physicians, nurses, and midwives, should maintain vigilance for depressive symptoms during the postpartum period.

Keywords: Postpartum depression, vaginal delivery, cesarean section, rates of postpartum depression

ÖZ

Amaç: Postpartum depresyon (PPD), doğumdan sonra ortaya çıkan önemli bir depresif bozukluktur. Geleneksel olarak doğumdan sonraki bir ay içinde ortaya çıkan majör depresif bozukluk olarak tanımlansa da, PPD hamilelik sırasında veya doğumdan sonraki ilk aydan sonra da ortaya çıkabilir. Gelişmiş ülkelerde kadınların yaklaşık %10-15'ini etkileyen PPD, hem anne hem de çocuk için ciddi sonuçlar doğurmaktadır. Bu çalışma, doğum şeklinin PPD için bir risk faktörü olup olmadığını değerlendirmek, doğum sonrası depresyon oranlarını belirlemek ve bu durumun farkındalığını artırmak amacıyla yapılmıştır.

Gereç ve Yöntemler: Bu prospektif kohort çalışması, 2025 yılının Mart ve Haziran ayları arasında hastanemizin Kadın Hastalıkları ve Doğum Anabilim Dalı'nda gerçekleştirilmiştir. Sezaryen veya vajinal doğum yapan ve doğumdan 7 ila 14 gün sonra doğum sonrası kontrollerine gelen kadınlar, Hasta Sağlığı Anketi-9 (PHQ-9) kullanılarak PPD açısından tarandı. Doğum grupları arasında klinik-demografik özellikler, PHQ-9 puanları ve PPD oranları karşılaştırıldı.

Bulgular: 289 katılımcıdan 67'si (%23,1) PPD taramasında pozitif sonuç aldı. PHQ-9 puanının ortalaması vajinal doğum grubunda 6,5, sezaryen grubunda ise 7,5 idi. PPD prevalansı vajinal doğum grubunda %25,4, sezaryen grubunda %19,8 idi. Bu farklılıklar istatistiksel olarak anlamlı değildi (sırasıyla p=0,628 ve p=0,268).

Sonuç: Toplumumuzda PPD prevalansı, literatürde bildirilen oranlarla aynı veya biraz daha yüksektir. Sezaryen doğum, PPD için ek risk oluşturmuyor gibi görünüyor. Anne, bebek ve aile üzerinde anne ruh sağlığının derin etkisi göz önüne alındığında, kadın doğum uzmanları, çocuk doktorları, aile hekimleri, hemşireler ve ebeler dahil olmak üzere sağlık hizmetleri sağlayıcıları, doğum sonrası dönemde depresif belirtilere karşı uyanık olmalıdır.

Anahtar Kelimeler: Postpartum depresyon, vajinal doğum, sezaryen, postpartum depresyon oranları

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INTRODUCTION

Postpartum depression (PPD) is a significant depressive disorder that occurs after childbirth (1). Although it is formally defined in psychiatric nomenclature as a major depressive episode occurring within one month of delivery, symptoms may also emerge during pregnancy or later in the postpartum period (2, 3). PPD not only impacts maternal health but also affects infant development and parenting behaviors (4). Suicide is the most severe complication of PPD, accounting for approximately 20% of maternal deaths in the first year postpartum—surpassing rates associated with postpartum hemorrhage and hypertensive disorders (5). Additionally, maternal depression can negatively affect children's behavioral, emotional, and cognitive development (6). Thus, identifying risk factors and developing prevention strategies for PPD is vital for both maternal and child well-being (7). The World Health Organization (WHO) strongly recommends routine screening and preventive measures for PPD (8).

PPD affects approximately 10–15% of women in developed countries, with prevalence rates reaching up to 20% in some populations (9). Among adolescent, unmarried, low socioeconomic status, poorly educated, or malnourished mothers, this rate may rise to 26% (10).

The pathophysiology of PPD is complex and not yet fully understood. However, biological, hormonal, genetic, and immune-related factors have been implicated (3). Some women may exhibit heightened sensitivity to hormonal changes during reproductive events such as menstruation, pregnancy, and menopause. The sudden decline in hormone levels after delivery is believed to be a major contributing factor (11, 12).

The American College of Obstetricians and Gynecologists recommends using the Edinburgh Postnatal Depression Scale for PPD screening. However, the Patient Health Questionnaire-9 (PHQ-9) is also considered a valid alternative (1). Randomized studies suggest that the optimal screening period is between 4 and 8 weeks postpartum, with even a single screening during this period proving more beneficial than none (13). Nevertheless, the ideal timing and frequency of screening remain undetermined (14).

Primary risk factors for PPD include a personal or family history of depression, whether perinatal or non-perinatal, and depression during pregnancy (15). Secondary risk factors include advanced maternal age, preterm birth, cesarean section, gestational diabetes, postpartum blues, stressful life events, poor social or marital support, low self-esteem, unplanned pregnancies, and difficult infant temperament (1).

If left untreated, PPD can result in detrimental outcomes for mothers, infants, and families. It is imperative that obstetricians screen for risk factors and symptoms using validated tools and collaborate with mental health professionals when necessary. This study aims to evaluate whether the mode of delivery is a risk factor for PPD, to assess postpartum depression rates, and to raise awareness of the condition.

MATERIAL AND METHODS

This prospective cohort study was conducted between March and June 2025 at the Gynecology and Obstetrics Clinic of Eskişehir City Hospital, a tertiary care center under the Ministry of Health of the Republic of Turkey. The PHQ-9 scale was used to screen for PPD in women who delivered vaginally or by cesarean section and presented for routine postpartum check-ups between 7 and 14 days after delivery. The PHQ-9 consists of nine items, each rated from 0 (not at all) to 3 (nearly every day), with total scores categorized as follows: 1–4 (minimal), 5–9 (mild), 10–14 (moderate), 15–19 (moderately severe), and 20–27 (severe depression) (16).

The PHQ-9 test in the PPD screening was used for screening purposes in its validated Turkish form developed by Sari et al (16, 17).

The required sample size was estimated using G*Power (version 3.1.9.7) for a two-proportion comparison (Chi-square test), assuming a 10% absolute difference in postpartum depression (PPD) prevalence between vaginal and cesarean deliveries (10% vs. 20%), with a significance level of 0.05 and power of 80%. This calculation indicated that a total of approximately 268 participants (134 per group) would be needed to detect this difference. Our study included 289 participants (173 vaginal, 116 cesarean), and a post-hoc power analysis showed an achieved power of approximately 75%, which was considered acceptable for detecting a moderate effect size (Cohen's $h \approx 0.32$).

Eligible participants were women who met the following inclusion criteria: no history of depression, whether perinatal or nonperinatal; no depressive symptoms during pregnancy; no significant maternal medical illnesses; absence of fetal anomalies; currently breastfeeding; and classified as having a low-risk obstetric profile.

Exclusion criteria included inability to read or write in Turkish, unwillingness to participate, presence of intellectual disabilities, or a diagnosis of a psychiatric disorder.

Demographic and clinical variables—including age, gravidity, parity, BMI, duration of marriage, gestational age at delivery, neonatal birth

weight, first- and fifth-minute APGAR scores, NICU admission rates, and PHQ-9 scores—were compared between the two groups. A PHQ-9 score ≥10 was used as the threshold for positive screening.

The study adhered to the ethical standards of the 2013 revision of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Eskişehir City Hospital (Approval Date: March 20, 2025; Decision No: ESH/BAEK 2025/140).

Statistical Analysis

Statistical analyses were conducted using SPSS version 30.0 (IBM Corp., Armonk, NY). Descriptive statistics were presented as means ± standard deviation (SD) or medians with interquartile ranges (IQR), depending on data distribution. Normality was assessed using the Shapiro-Wilk test. Independent samples t-test was used for normally distributed continuous variables, and the Mann-Whitney U test for non-normal data. Categorical variables were compared using Chi-square or Fisher's exact test where appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 289 participants were included in the study: 173 delivered vaginally, and 116 underwent cesarean section. Participants in the vaginal delivery group were significantly younger, with lower gravidity, parity, and shorter duration of marriage compared to the cesarean group ($p<0.01$ for all).

Overall, 67 of the 289 participants (23.1%) screened positive for PPD based on PHQ-9 scores. Term delivery occurred in 88.4% of the vaginal birth group and 76.7% of the cesarean group ($p<0.01$). No statistically significant differences were found between the two groups in terms of neonatal weight, APGAR scores, or NICU admission rates.

The median PHQ-9 score was 6.5 for the vaginal delivery group and 7.5 for the cesarean section group. PPD rates were 25.4% and 19.8%, respectively. However, these differences were not statistically significant ($p = 0.628$ and $p = 0.268$, respectively).

The results of the comparison of clinicodemographic characteristics, neonatal outcomes, PHQ-9 scores and postpartum depression rates between the groups are presented in Table 1.

DISCUSSION

The arrival of a new child is generally expected to bring joy to the mother and family. However, due to a combination of genetic, epigenetic, environmental, biochemical, and hormonal factors, up to 25% of women may develop depressive symptoms postpartum (6). If unrecognized or untreated, PPD can have serious consequences for the entire family unit. Recognizing and managing primary risk factors such as prior depression or depression during pregnancy is crucial (1).

Table 1. Comparison of demographic, obstetric, and neonatal characteristics between vaginal and cesarean delivery groups

Variable	Vaginal Delivery (n = 173)	Cesarean Delivery (n = 116)	p-value	Statistical Test
Age (years)	26 [9.5]	30 [6.75]	**0.001**	Mann–Whitney U
Gravida	2 [2]	2 [1]	**0.007**	Mann–Whitney U
Parity	1.5 [1]	2 [2]	**0.005**	Mann–Whitney U
BMI (kg/m²)	27.97 [5.82]	29.05 [6.44]	0.110	Mann–Whitney U
Duration of marriage (years)	3 [5.75]	4 [5]	**0.001**	Mann–Whitney U
Gestational age >37 weeks	153 (88.4%)	89 (76.7%)	**0.008**	Chi-square test
Birth weight (g)	3100 [457.5]	3130 [1015]	0.447	Mann–Whitney U
1-minute APGAR score	9 [0]	9 [0]	0.062	Mann–Whitney U
5-minute APGAR score	10 [0]	10 [0]	0.061	Mann–Whitney U
NICU admission (Yes)	35 (20.2%)	34 (29.3%)	0.076	Chi-square test
PHQ-9 score	6.5 [7.75]	7.5 [8]	0.628	Mann–Whitney U
PPD positive (%)	44 (25.4%)	23 (19.8%)	0.268	Chi-square test

- Continuous variables are presented as median [interquartile range] (IQR) due to non-normal distribution (as determined by the Shapiro–Wilk test).
- Categorical variables are expressed as n (%).
- p-values < 0.05 were considered statistically significant.

Although the PHQ-9 scores were slightly higher in the cesarean section group, the difference was not statistically significant. This aligns with prior literature indicating an estimated PPD prevalence of 10–20%, though cultural variation is considerable (6). Even with the exclusion of major risk factors, our observed prevalence was on the higher end.

Numerous epidemiological studies have examined the association between cesarean section and the risk of postpartum depression (PPD), but the findings remain inconsistent (18). For example, Carter et al. conducted a meta-analysis of 24 studies in 2006 and found no significant relationship between cesarean delivery and PPD (20). In contrast, a 2017 meta-analysis by Xu Hui and colleagues, which included 20 studies, reported an increased risk of PPD following cesarean delivery—particularly in cases of emergency cesarean section. However, the increased risk associated with elective cesarean section did not reach statistical significance (19).

Xu Hui et al. attributed the discrepancy between their findings and those of Carter et al. to differences in methodology. Specifically, Carter and colleagues examined the impact of emergency versus elective cesarean sections separately in only eight of their included studies, which may have limited their ability to detect nuanced associations. In our study, similar to Carter et al., we did not differentiate between emergency and elective cesarean deliveries, which we believe is a key factor contributing to our differing results from those reported by Xu Hui and colleagues.

Several other methodological differences may also explain the discrepancy. Xu Hui's meta-analysis comprised heterogeneous studies with varying designs and quality. Additionally, many of the included studies conducted PPD screening later in the postpartum period than our study, and the majority used the Edinburgh Postnatal Depression Scale (EPDS), whereas we used the PHQ-9. Variations in screening tools, cutoff scores, and the timing of assessments may significantly influence PPD prevalence estimates and comparability across studies. Furthermore, important limitations of Xu Hui's meta-analysis should be noted: (1) confounding variables were adjusted inconsistently across studies; (2) the EPDS cutoff values used to define PPD varied substantially; and (3) many studies did not clearly distinguish whether elective cesarean sections were performed for medical indications or maternal request, which could significantly influence maternal psychological outcomes (19).

Strengths of this study include its prospective design and administration of the PHQ-9 face-to-face by clinical staff. Limitations include the relatively small sample size and early screening period (7–14 days after birth), which may result in cases developing two weeks or later being missed.

CONCLUSION

Our findings suggest that cesarean delivery is not an independent risk factor for postpartum depression. The observed prevalence of PPD was within or slightly above reported global ranges. Given the substantial burden of untreated maternal mental illness on mothers, infants, and families, all healthcare providers involved in postpartum care—including obstetricians, pediatricians, family physicians, nurses, and midwives—should remain vigilant in recognizing symptoms of depression.

Further studies with larger sample sizes and longer follow-up periods are needed to validate these findings.

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Eskişehir City Hospital (Approval Date: March 20, 2025; Decision No: ESH/BAEK 2025/140).

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Conflict of Interest: The authors declare no conflict of interest for this article.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Are Decisions About Cesarean Deliveries Affected by Litigation Fears or Economic Expectations?

Sezaryen Doğum Kararları Dava Korkusundan mı Yoksa Ekonomik Beklentilerden mi Etkileniyor?

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ABSTRACT

Aim: Annually, approximately 20 million pregnant women undergo cesarean sections worldwide. However, a global trend of increasing cesarean section rates has been observed. The objective of this study is to evaluate which factors affect the decision of physicians to perform cesarean sections, with the exception of the actual indications for such procedures.

Material and Methods: Data were collected using questionnaires that were delivered through the internet and telephone. The questionnaires consisted of 24 questions, including age, year of professional experience, institution, working conditions, and economic expectations.

Results: The present study included 327 clinicians. The findings indicate that clinicians, particularly physicians working in the private sector (62.9% vs. 21.2%, p<0.001), may be influenced by pregnant women's preferences regarding the mode of delivery especially sezaryen section. Furthermore, the data indicates a significant disparity in the rates of vaginal birth among clinicians in different sectors, with a higher proportion of clinicians in private practice (3.2%) compared to public health facilities (7.3%), a difference that is statistically significant at the p<0.001 level. The study revealed no statistically significant differences between the private and public sectors, between legal issues, or between maternal and fetal fears (p>0.05).

Conclusion: Despite the abundance of recommendations and methodologies, the upward trend in CS rates persists. Improving national health policies, addressing physicians concerns regarding legal issues, and having healthcare professionals guide mothers birth preferences toward vaginal delivery within indications may contribute to reducing cesarean rates.

Keywords: Cesarean section (CS), decision of the birth type, litigation, maternal willing

ÖZ

Amaç: Dünya genelinde her yıl yaklaşık 20 milyon hamile kadın sezaryen ameliyatı geçirmektedir. Bununla birlikte, sezaryen oranlarında küresel bir artış eğilimi gözlenmektedir. Bu çalışmanın amacı, bu tür prosedürler için gerçek endikasyonlar dışında, hekimlerin sezaryen yapma kararını etkileyen faktörleri değerlendirmektir.

Gereç ve Yöntemler: Veriler internet ve telefon aracılığıyla dağıtılan anketler kullanılarak toplanmıştır. Anketler yaş, mesleki deneyim yılı, çalışılan kurum, çalışma koşulları ve ekonomik beklentileri içeren 24 sorudan oluşmuştur.

Sonuçlar: Bu çalışmaya 327 klinisyen katılmıştır. Bulgular, klinisyenlerin, özellikle özel sektörde çalışan hekimler arasında (%62,9'a karşı %21,2, p<0,001) gebe kadınların doğum şekline ilişkin tercihlerinden etkilenebildiklerini göstermiştir. Ayrıca, veriler farklı sektörlerdeki klinisyenler arasında vajinal doğum oranlarında önemli bir eşitsizlik olduğunu göstermektedir; özel muayenehanelerde çalışan klinisyenlerin oranı (%3,2) kamu sağlık tesislerinde çalışanlara (%7,3) kıyasla daha yüksektir ve bu fark p<0,001 düzeyinde istatistiksel olarak anlamlıdır. Çalışmada özel ve kamu sektörleri arasında, hukuki vakalar arasında veya anne ve fetüs korkuları arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p>0,05).

Sonuç: Çok sayıda öneri ve metodolojiye rağmen, sezaryen oranlarındaki artış eğilimi devam etmektedir. Ulusal sağlık politikalarının iyileştirilmesi, hekimlerin hukuksal konulardaki endişelerinin giderilmesi, annelerin doğum tercihlerinin endikasyon dahilinde sağlık profesyonellerince vajinal doğuma yönlendirilmesi, sezaryen oranlarının düşürülmesine katkıda bulunabilir.

Anahtar Kelimeler: Sezaryen (CS), doğum şekline karar verme, dava açma, annenin isteği

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INTRODUCTION

Globally, approximately 20 million pregnant women undergo cesarean sections each year (1). At least 35% of these procedures are considered as "without medical indication", offering no additional benefit for maternal or neonatal outcomes; nevertheless, cesarean rates continue to rise worldwide (2). In some countries, the cesarean section rate approaches 50%, far exceeding the World Health Organization's recommended threshold of 15% (3).

This rising incidence of cesarean section all over the world is not considered to be associated with actual medical or obstetrical indications. Nevertheless, it is concerned with both maternal and obstetricians' attitudes and options (1, 2, 4-7). The major reason for maternal request on cesarean section was fear of childbirth (8). Also, in Spain and Italy, fear of litigation had effect on obstetricians' decision to accept the maternal request. Thus, the obstetricians were more frequently seen to perform cesarean section (9). In this study of eight European countries, obstetricians in two European countries had no fear of lawsuits after vaginal birth (VB) complications. However, obstetricians in six other European countries have faced lawsuits (9).

In Italy, Spain, and Luxembourg, obstetricians have been more actively involved in the private sector compared to other countries. These three countries also report higher cesarean section rates than other European nations (9). In this study, this finding is examined in light of factors such as fear of litigation, maternal request, and the influence of working predominantly in the private sector.

The present study aims to explore obstetricians' views on performing cesarean sections based on non-medical indications, particularly focusing on maternal requests, fear of litigation, and economic expectations that may influence their decision-making in Türkiye. Our hypothesis suggests that the fear of lawsuits would not significantly influence clinicians' decisions to perform cesarean sections in the absence of clinical indications.

MATERIALS AND METHODS

This questionnaire-based randomised survey of obstetricians' indications for caesarean section in Türkiye was conducted between April and June 2018. Data were collected using printed forms completed in person (n = 124) and via email (n = 193) through internet communication, according to the convenience of the participating obstetricians. Ethical approval for the study was obtained (04.26.2018/707).

The present study aims to clarify obstetricians' views and behaviors regarding requests for cesarean section from pregnant women with a single fetus, at term, in cephalic presentation, and with a normal estimated fetal weight (measured by ultrasound), but without a clinical indication. Obstetricians who only treat gynecological patients and do not perform vaginal or cesarean deliveries were excluded from the study.

The first part of the questionnaire focused on demographic information of the respondents, including age, years of clinical experience (categorized as less than or more than 15 years-Ülkemizdeki eski ve yeni hukuksal düzenlemeleri yaşayarak deneyimleyen hekimleri çalışmaya almak istedik.Ayrıca cerrahi deneyim, hekimliğe bakış yönünden meslekteki sürenin farklı bakış açıları getireceğinden 15 yıllık deneyim düşünüldü.), characteristics of the institution where they work (e.g., public or private sector, night shifts, on-call duty), parental status and the mode of delivery for their own children, and the average monthly number of vaginal and cesarean deliveries at their institution.

The second part of the questionnaire evaluated the potential differences between obstetricians working in the private and public sectors in terms of their reasons for performing cesarean sections without medical indication. This section included questions about the most influential fears leading to cesarean decisions, whether they had faced legal proceedings or institutional investigations, the frequency of maternal requests for cesarean sections, the most common Subobjective indicated causes CS, and the impact of economic expectations or job satisfaction on their decision to pursue a career in obstetrics. Monthly figures for vaginal and cesarean births were also compared.

Statistical Analysis

Statistical package program SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data in this study. Data were expressed in percentages. Relationships between categorical variables were analyzed using the Chi-square test. $p<0.05$ was accepted as statistically significant.

RESULTS

Demographic characteristics of the participants are presented in Table 1. In our study, physicians working in private clinics were significantly more likely to accept cesarean section requests from pregnant women compared to those working in public institutions (62.9% vs. 21.2%, $p<0.001$). Economic expectations were also significantly higher among physicians in the private sector (82.3% vs. 59.4%, $p<0.001$). A significant difference was observed between public and private sector clinicians in terms of never

Table 1. Demographic features

		n	(%)
Age (years)			
	<50	258	81.4
	>50	59	18.6
Years in the profession			
	<15	217	68.5
	>15	100	31.5
Institute			
	Public	193	61.1
	Private	123	38.9
Delivery Method of the Physician's Child			
	No	69	21.8
	VB	44	13.9
	CS	176	55.5
	BOTH	28	8.8
The way you work			
	Nightshift	142	44.8
	Oncallduty	127	40.1
	Neither of two	48	15.1
Your reason to choose an obstetrician			
	High income	139	44.0
	Tuspoint	52	16.5
	Ideals	125	39.6
VB count per month			
	No	18	5.7
	1-40	220	69.4
	>40	79	24.9
CS count per month			
	1-40	253	79.8
	>40	64	20.2

CS, cesarean section;VB, Vaginal Birth

Table 2. Variables categorized to the type of the institution

		Public % (n)	Private % (n)	p
Reason for CS preference				
	Hypoxic delivery	62.2 (120)	52.4 (65)	0.209
	Brachial plexus/dystocia	7.3 (14)	10.5 (13)	
	Uterine atony	30.6 (59)	37.1 (46)	
Internal investigation				
	Yes	50.3 (97)	44.4 (55)	0.304
	No	49.7 (96)	55.6 (69)	
Medicolegal Litigation				
	Yes	88.1 (170)	87.9 (109)	0.962
	No	11.9 (23)	12.1 (15)	
Acceptance of the patient's CS request				
	Often-usually	21.2 (41)	62.9 (78)	<0.001
	Sometimes	40.4 (78)	22.6 (28)	
	Rare-no	38.3 (74)	14.5 (18)	
Subobjective indicated causes CS				
	Medicolegal litigation fear	74.6 (141)	64.5 (78)	0.107
	Time pressure	3.2 (6)	2.5 (3)	
	Patient's preference	22.2 (42)	33.1 (40)	
Reason for preferring obstetrics				
	High income	59.4 (114)	82.3 (102)	<0.001
	Special interest	40.6 (78)	17.7 (22)	
VB count per month				
	No	7.3 (14)	3.2 (4)	<0.001
	≤40	55.4 (107)	91.1 (113)	
	>40	37.3 (72)	5.6 (7)	
CS count per month				
	≤40	77.2 (149)	83.9 (104)	0.149
	>40	22.8 (44)	16.1 (20)	

CS, cesarean section;VB, Vaginal Birth

having perform a VB count per month (7.3% vs. 3.2%, respectively; $p < 0.001$). However, no significant difference was found between the two groups regarding maternal-fetal or legal issues in applying cesarean indications (p>0.05) (Table 2).

The present study revealed no statistically significant differences with regard to maternal request cesarean sections, clinicians' apprehensions regarding the administration of cesarean sections due to maternal-fetal complications, economic expectations, and forensic concerns across varying experience levels (less than 15 years versus more than 15 years) and age groups (less than 50 years versus more than 50 years) (p>0.05) (Table 3).

DISCUSSION

The cesarean section rate in Türkiye was 14.3% in 1993 and increased to 51.9% by 2013 (3), despite efforts by the Ministry of Health to reduce it. Our findings indicate that more than 10% of all clinicians do not perform vaginal births among term pregnant women. Globally, the rate of high-compensation lawsuits has risen rapidly in recent years, which may play a significant role in the increasing prevalence of cesarean deliveries (10). Another finding reveals that, despite advanced age and professional experience, some clinicians still refrain from performing vaginal births.The incidence of obstetric complications during labor or delivery is estimated to be between 2% and 2.8%, with 27.7% of those cases

Table 3. Influence of age and professional years

		≤50 age % (n)	>50 age % (n)	p	≤15year % (n)	>15year % (n)	p
Cs preference is also your active concern				0.269			0.228
	Anoxic delivery	58.1 (150)	59.3 (35)		60.8 (132)	53.0 (53)	
	Brachial plexus, dystocia	9.7 (25)	3.4 (2)		6.9 (15)	12.0 (12)	
	Uterine atony	32.2 (83)	37.3 (22)		32.3 (70)	35.0 (35)	
Internal investigation				0.284			0.799
	Yes	46.5 (120)	54.2 (32)		47.5 (103)	49.0 (49)	
	No	53.5 (138)	45.8 (27)		52.5 (114)	51.0 (51)	
Oyer				0.070			0.713
	Yes	86.4 (223)	94.9 (56)		87.6 (190)	89.0 (89)	
	No	13.6 (35)	5.1 (3)		12.4 (27)	11.0 (11)	
Acceptance of the patient's cs request				0.802			0.355
	Often-usually	37.6 (97)	37.3 (22)		35.0 (76)	43.0 (43)	
	Sometimes	34.1 (88)	30.5 (18)		35.5 (77)	29.0 (29)	
	Rare-no	28.3 (73)	32.2 (19)		29.5 (64)	28.0 (28)	
Subobjective indicated causes				0.417			0.408
	Forensicfear	71.8 (181)	65.5 (38)		72.8 (155)	66.0 (64)	
	Time anxiety	2.4 (6)	5.2 (3)		2.3 (5)	4.1 (4)	
	Patient preference and fear	25.8 (65)	29.3 (17)		24.9 (53)	29.9 (29)	
Your reason for preference for obstetrics				0.078			0.227
	High income	66.1 (170)	78.0 (46)		66.2 (143)	73.0 (73)	
	Obstetric request	33.9 (87)	22.0 (13)		33.8 (73)	27.0 (27)	
NSD count per month				0.122			0.003
	No	5.0 (13)	8.5 (5)		4.6 (10)	8.0 (8)	
	≤40	67.8 (175)	76.3 (45)		65.0 (141)	79.0 (79)	
	>40	27.1 (70)	15.3 (9)		30.4 (66)	13.0 (13)	
CS count per month				0.743			0.955
	≤40	79.5 (205)	81.4 (48)		79.7 (173)	80.0 (80)	
	>40	20.5 (53)	18.6 (11)		20.3 (44)	20.0 (20)	

CS, cesarean section;VB, Vaginal Birth

linked to obstetric negligence (11). Fewer than half of the cases involving negligent obstetric injury result in indemnity payments (11). Many obstetricians believe that cesarean delivery reduces the risk of legal action (11). Consequently, while the rate of vaginal birth after cesarean (VBAC) increased between 1981 and 1995, it subsequently declined due to a surge in lawsuits (11). In 2008, it was estimated that 2.9 million cesarean sections were performed unnecessarily (12).

Our hospital is a tertiary referral center and the second largest maternity hospital in Türkiye, with an average of 16,000 to 18,000 deliveries annually. Forceps deliveries are not performed, and the vacuum delivery rate was just 0.003 in 2014. These figures support our finding that most obstetricians avoid using vacuum or forcepsassisted delivery. According to our survey, the primary reason for this reluctance appears to be the prevalence of malpractice lawsuits related to non-medically indicated cesarean sections among both private and public sector physicians.

In 2006, legal reforms facilitated the filing of malpractice lawsuits against physicians, which may have contributed to the increase in cesarean section rates in Türkiye. Similar trends are observed in European countries such as Italy, France, Germany, Luxembourg, and Spain, where malpractice lawsuits are common and fear of litigation often leads obstetricians to choose cesarean delivery without medical necessity (9). In contrast, in countries like Sweden

and the Netherlands, where there are no lawsuits related to post-birth complications, obstetricians face less legal pressure and cesarean rates are lower (9).

In Türkiye, the public requires physicians to carry medical malpractice insurance to protect themselves from compensation claims. Obstetricians, being part of a high-risk group, pay high premiums for such coverage. However, the compensation amounts awarded in lawsuits often exceed the insurance premiums paid. Therefore, we are in the opinion that new legislative approaches regarding malpractice lawsuits are necessary to help reduce the cesarean section rate in Türkiye.

Currently, economic expectations among obstetricians, particularly those working in public institutions, are not as high. A decade ago, obstetricians were allowed to work simultaneously in both private clinics and public hospitals. However, this dual practice is no longer permitted due to legal restrictions. In our questionnaire, a greater proportion of physicians working in the private sector reported choosing the obstetrics profession due to economic expectations compared to those in the public sector (82.3% vs. 59.4%). Cesarean section rates among pregnant women were significantly higher in the private sector than in public institutions (1, 5, 13, 14). Obstetricians working in private institutions are more likely to consider maternal request for cesarean section as a valid indication, even in the absence of a clinical necessity (5). Additionally, cesarean section rates were lower among pregnant women with lower socioeconomic status (2, 13, 15). In South Asian and sub-Saharan African countries, cesarean section rates were highest among the urban wealthy and lowest among the rural poor (12).

In our questionnaire, maternal request for cesarean delivery was reported in 62.9% of cases in the private sector and 21.2% in the public sector. Maternal request is considered a major factor contributing to the rising cesarean section rates (6); however, clinicians' attitudes may significantly influence maternal preferences regarding the mode of delivery (9, 13). Reasons cited for maternal request include fear of childbirth and pain, prolonged labor, anticipated physical trauma, concerns about vaginal tonicity and urinary incontinence, previous traumatic birth experiences, conception via assisted reproductive technologies, and efforts to protect the baby from vaginal birth-related trauma. Despite the increase in cesarean section rates, there has been no corresponding decline in the incidence of neonatal seizures or cerebral palsy in term births (16). In fact, elective cesarean deliveries are associated with higher rates of neonatal respiratory complications, delayed initiation of breastfeeding, and neonatal morbidity (15, 16). Moreover, cesarean section offers no advantage in reducing pelvic floor disorders compared to spontaneous vaginal delivery, and it increases the risk of peripartum emergency hysterectomy, placenta previa, placental adhesion disorders, scar dehiscence, and pelvic adhesions (18). Despite these risks, 17% of obstetricians in London and 46.2% in North America reported willingness to perform elective cesarean sections for an uncomplicated, term, cephalic pregnancy based on maternal or spousal request rather than clinical indications (19). In Denmark, only 1.1% of obstetricians reported preferring elective cesarean section in uncomplicated pregnancies; however, approximately 40% agreed that women have the right to request an elective cesarean without clinical justification (19). Another contributing factor is the estimated fetal weight: higher fetal weight often increases obstetricians' inclination toward cesarean delivery, driven by a desire to prevent fetal injury, perineal trauma, and future urinary or fecal incontinence. (5,19).

The primary limitation of this study was the absence of a question regarding clinicians' experience with instrumental deliveries, such as vacuum or forceps-assisted births. We believe that many clinicians may not have been able to respond to such questions accurately. Additionally, data were collected from various regions across Türkiye, which is important given that cultural attitudes toward childbearing and the number of children vary significantly between regions. Another limitation is that the questionnaire did not include questions about the use of epidural anesthesia, which may have influenced our findings. Furthermore, institutions were not categorized as university hospitals or training and research (tertiary) hospitals, which may have introduced institutional variation. Finally, the question concerning economic expectations was not asked in a direct and detailed manner.

While further research is necessary to further reduce the cesarean delivery rate, it is hoped that this study will make a positive contribution to the existing literature.

Ethics Committee Approval: Ethical approval for the study was obtained: Ministry of Health, Health Sciences University, Etlik Zübeyde Hanım Women's Diseases Training and Research Hospital, Medical Specialization Training Board Presidency (04.26.2018/707).

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Outcomes of Unplanned Vaginal Birth after Caesarean Section in a Secondary Care Hospital, Southern Türkiye

Güney Türkiye'de İkinci Basamak Bir Hastanede Sezaryen Sonrası Planlanmamış Vajinal Doğum Sonuçları

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ABSTRACT

Aim: To evaluate the demographic and obstetric characteristics of patients who had never visited our clinic for examination and underwent unplanned vaginal birth after cesarean section in our clinic, and to discuss the fetomaternal risks.

Materials and Methods: This is a retrospective study including a total of 285 pregnant women who presented to the delivery room with spontaneous onset of labor, had at least one previous cesarean section, and underwent unplanned vaginal birth after cesarean section at Kilis State Hospital between January 2015 and December 2020.

Results: In our study, the mean maternal age (±SD) was 28.4 ± 5.4 years, gestational age (±SD) was 37.0 ± 3.5 weeks, birth weight (±SD) was 3024 ± 689 g, and the median delivery time was 110 (20–150) minutes. In the study, 264 patients (92.6%) successfully delivered vaginally after cesarean section. A total of 27 patients (9.5%) developed postpartum complications.

Conclusion: In patients who have had a previous cesarean section and present to the delivery room for spontaneous vaginal birth in the active phase of labor, cesarean section rates can be reduced by performing vaginal delivery with close follow-up when appropriate patient selection, adequate clinical infrastructure, and a mutual patient–physician agreement are provided.

Keywords: Cesarean section, VBAC, refugees, migration, vaginal birth

ÖZ

Amaç: Kliniğimize daha önce hiç muayene için gelmemiş ve kliniğimizde sezaryen sonrası plansız vajinal doğum yapmış hastaların demografik ve obstetrik özelliklerini değerlendirmek ve feto-maternal riskleri tartışmak.

Gereç ve Yöntemler: Bu çalışma Ocak 2015-Aralık 2020 tarihleri arasında Kilis Devlet Hastanesi'nde spontan doğum ağrısı ile doğumhaneye başvuran, daha önce en az 1 kez sezaryen olan ve sezaryen sonrası plansız vajinal doğumu tercih eden toplam 285 gebeyi kapsayan retrospektif bir çalışmadır.

Bulgular: Çalışmamızda ortalama anne yaşı (±SD) 28,4 ±5,4 yıl, gebelik yaşı (±SD) 37,0 ±3,5 hafta, doğum ağırlığı (±SD) 3024 ±689 g ve ortanca doğum süresi 110 (20-150) dakika idi. Çalışmada 264 hasta (%92,6) sezaryen sonrası vajinal yolla başarılı bir şekilde doğum yaptı. Toplam 27 hastada (%9,5) doğum sonrası komplikasyon gelişti.

Sonuç: Daha önce sezaryen geçirmiş ve doğumun aktif fazında spontan vajinal doğum için doğumhaneye başvuran hastalarda uygun hasta seçimi, gerekli klinik altyapı ve istekli hasta-hekim ilişkisi sağlandığında yakın takip ile vajinal doğum gerçekleştirilerek sezaryen oranları azaltılabilir.

Anahtar Kelimeler: Sezaryen, SSVD, mülteci, göçmenlik, vajinal

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INTRODUCTION

Recently, cesarean section (CS) rates have been increasing rapidly worldwide due to maternal preference and medico-legal concerns (1). A history of CS appears to be an important factor in the observed increase (2). The increase in CS rates has become a global concern due to serious fetomaternal risks (3, 4). In order to reduce both fetomaternal risks and the financial burden on governments, the concept of vaginal birth after cesarean section (VBAC) emerged, and its implementation began in the early 1980s. During that time frame, VBAC became more common, but serious complications were reported following the procedure. Due to these complications and the accompanying malpractice lawsuits, there was a rapid decrease in the number of VBACs (5). For this reason, many cross-sectional studies have been conducted to predict the success of VBAC (5, 6). Having a previous lower uterine segment transverse incision and a history of prior vaginal birth are the most important factors that increase the success of VBAC (2). VBAC rates vary significantly between countries, ranging from 9.6% to 52.2% (7). According to clinical guidelines, for births following cesarean section, VBAC can be considered (8). Regarding labor management, pregnant women with spontaneous onset of labor have a higher chance of vaginal birth and a lower risk of uterine rupture. Therefore, VBAC is often recommended for pregnant women with spontaneous labor (2). According to the literature, the success rate of VBAC is expected to be between 60% and 80% (5). In this context, we aimed to evaluate the demographic and obstetric characteristics of patients who underwent unplanned VBAC in our clinic and to determine the fetomaternal risks, given the limited number of publications documenting the success of unplanned VBAC in unfollowed pregnancies in our country.

MATERIALS AND METHODS

This study is a retrospective descriptive study including the medical records of patients who underwent unplanned VBAC between January 2015 and December 2020 at the Kilis State Hospital, Department of Obstetrics and Gynecology.

A total of 468 patients were admitted to our clinic for attempted VBAC over a 6-year period. Among these, 308 patients who presented to the labor ward with spontaneous onset of labor and underwent unplanned VBAC were included in the study. Complete delivery data were not available for 17 of these 308 patients and cervical length could not be measured in 6 patients because they were in full cervical dilatation at presentation; therefore, a total of 23 patients were excluded from the analysis. As a result, the study was completed with 285 patients. Our center is located in a developing (OECD) country on the southern border, and provides healthcare services to a large number of Syrian refugees affected by the Syrian civil war. Due to this situation, pregnant refugee patients were often unable to attend pregnancy check-ups and routine follow-ups. For this reason, and because these patients were admitted to our hospital during active labor, we were unable to access previous operative notes for many of them. As a result, patients who had never visited our hospital for routine prenatal follow-up, who were not evaluated for VBAC eligibility in outpatient settings, and who presented to the delivery room in active labor were admitted for unplanned VBAC without knowledge of the type or location of the previous cesarean scar.

In our study, unplanned VBAC was defined as the situation in which refugee and local patients who had no previous access to healthcare services and had never undergone antenatal examination presented with active labour. This definition aligns with the criteria used by Assmani and Hassan, who classified similar cases without prior antenatal planning as “unplanned VBAC”(9). In a significant portion of our patient population—especially among refugees—previous CS reports were inaccessible due to the lack of routine antenatal follow-up. Despite the absence of operative notes, all patients were clinically assessed on admission for VBAC eligibility, including lower uterine segment thickness and fetal presentation. Patients and their families were clearly informed about the potential risks, particularly uterine rupture, and written informed consent was obtained. This approach is supported by recent RCOG guidelines, which state that VBAC can be offered even when the type of uterine incision is unknown, provided there are no contraindications and appropriate infrastructure is available(10). At our institution, clinical decisions in such cases are made individually, considering patient profile and current conditions. Each patient was evaluated for fetal presentation, uterine tenderness, scar-related findings, and cervical dilatation. Labour was monitored continuously, and a 24/7 surgical team was available for emergency cesarean if needed.

Although the study is retrospective in nature, the data collection process was conducted in a systematic and consistent manner. All data were retrieved from the hospital’s electronic medical records and delivery room logs, which include standardized fields for maternal demographics, obstetric history, delivery progress, interventions, and neonatal outcomes. Two independent researchers reviewed the records to ensure accuracy, and discrepancies were resolved through consensus. Cases with missing or inconsistent data were excluded from the final analysis to preserve data quality.

Pregnant women between 24 and 42 weeks of gestation, with cephalic presentation, with or without a history of previous vaginal birth, and with or without premature rupture of membranes, were

included in the study. Exclusion criteria included maternal age under 18 years, more than three previous cesarean sections, placenta previa, placental invasion anomalies, malpresentation, initial hemoglobin value below 7 g/dL, and a history of previous uterine rupture.

Initial detailed evaluations were performed for each patient at the time of admission. During transvaginal ultrasonography (USG), the myometrial thickness of the lower uterine segment was assessed.

Maternal age, birth weight, and 1st and 5th minute Apgar scores were considered as both categorical and continuous variables. The mean and standard deviation (SD) were reported for continuous variables with normal distribution. The median and interquartile range (IQR; Q1–Q3) were reported when the SD exceeded the mean. Categorical variables in our study included: birth weight (< 2500 g, 2500–3900 g, ≥ 4000 g), 1st and 5th minute Apgar scores (≤ 6, 7–10), maternal age (< 35, ≥ 35), parity (1, 2, 3, 4, 5+), previous CS indications, pregnancy interval (< 24 months, ≥ 24 months), lower uterine segment thickness (< 2 mm, ≥ 2 mm), cervical dilatation (4 < x < 6 cm, ≥ 6 cm), and preoperative–postoperative hemoglobin difference (< 2 g/dL, ≥ 2 g/dL).

Ethics Committee

Ethical approval for this study was obtained from Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee with the decision number 22-KAEK-058 dated 17.03.2022. The study was conducted in accordance with the Helsinki Declaration.

Statistical Analysis

Frequencies and percentages were calculated for categorical variables. Analysis of all variables was done with R Studio 2022.07.2 Build 576.

Table 1. Sociodemographic and Obstetric Characteristics

	(n=285)	(%)
Gestational week		
Median (IQR)	37(±3.5)	
Previous Cesarean Indications		
Placental abruption	36	12.6
Fetal distress	150	52.6
Non-progressive labor	51	17.9
Breech presentation	12	4.2
Transverse lie	9	3.2
Macrosomia	12	4.2
Previa	12	4.2
Triplet pregnancy	3	1.1
Previous Vaginal Birth		
Present	207	72.6
Absent	78	27.4
Pregnancy Interval		
< 24 months	168	58.9
≥ 24 months	117	41.1
Race		
Turkish	57	20
Syrian	228	80
Lower Uterine Segment Thickness		
< 2 mm	9	3.2
≥ 2 mm	276	96.8
Cervical Dilatation		
4 < x < 6 cm	117	41.1
≥ 6 cm	168	58.9
Spontaneous Membrane Rupture		
Present	120	42.1
Absent	165	57.9
VBAC success		
Successful	264	92.6
Failed	21	7.4

Data are presented as n (%) or median [IQR], Abbreviations: IQR: Interquartile Range, VBAC: Vaginal Birth After Cesarean

RESULTS

A total of 285 patients with at least one previous CS were included in the study. Of these, 264 patients had one, 9 had two, and 12 had three previous cesarean sections. In terms of nationality, 228 patients were Syrian and 57 were Turkish citizens. Among the 285 patients, 207 had a history of prior vaginal birth. Six of the patients with two previous cesarean sections and three of the patients with three previous cesarean sections had a history of vaginal delivery and ultimately achieved a successful VBAC. Of the 21 Turkish patients who experienced failed VBAC, 15 underwent CS due to non-progressive labor, and 6 due to fetal distress (Table 1).

In our study, the mean maternal age was 28.4 ± 5.4, gestational age was 37.0 ± 3.5 weeks, birth weight was 3024 ± 689 g, and the median labor duration was 110 (20–150) minutes (Tables 1, 2, and 3). All 285 patients who underwent VBAC presented to our clinic with spontaneous labor during the second (active) phase of the first stage of labor (cervical dilatation > 4 cm). Table 2 presents the data on maternal outcomes.

All patients had a cervical dilatation of at least 4 cm at the time of admission to the delivery room. Labor induction was not initiated for any patient. Spontaneous rupture of membranes occurred in 120 patients. The remaining 165 patients underwent amniotomy at 5 cm of cervical dilatation to accelerate labor. Only 12 patients reported pain at the site of the previous uterine incision. In 9 patients, the myometrial thickness was less than 2 mm at admission. These patients underwent VBAC under close monitoring. The mean difference in hemoglobin levels between admission and the 6th

Table 2. Maternal Outcomes

	n=285	(%)
Maternal age(years)		
<35	237	83.1
35<	48	16.9
Preop-Postop Hb Difference (g/dL)		
< 2	192	67.4
≥ 2	93	32.6
Labor Duration (minutes)		
Median (IQR)	110 (20-150)	
Complication		
Present	27	9.5
Placental retention	6	2.1
Postpartum endometritis	3	1.1
Blood transfusion	9	3.2
intravenous ferric carboxymaltose	9	3.2
Absent	258	90.5

Data are presented as n (%) or median [IQR, Abbreviations: IQR: Interquartile Range, Hb: Hemoglobin

postpartum hour was 1.5 ± 1.0 g/dL. Placental retention developed in 6 (2.1%) patients, and postpartum endometritis developed in 3 (1.1%) patients. During the postpartum period, appropriately crossmatched erythrocyte suspension and fresh frozen plasma were administered to 9 (3.2%) patients, and intravenous ferric carboxymaltose was given to another 9 (3.2%) patients. Neonatal outcomes, including Apgar scores, are presented in Table 3.

Table 3. Neonatal Outcomes

	n=285	(%)
Birth Weight		
< 2500	30	10.5
2500-3900	249	87.4
≥ 4000	6	2.1
Mean ± SD	3024 ± 689.2	
1-minute Apgar Score		
≤ 6	21	7.4
7-10	264	92.6
Mean ± SD	8.2 ± 1.8	
5-minute Apgar Score		
≤ 6	15	5.3
7-10	270	94.7
Mean ± SD	9.5 ± 1.9	

Data are presented as n (%) or mean ± SD, Abbreviations: SD: Standard Deviation

DISCUSSION

Although studies on VBAC have been conducted worldwide to reduce CS rates, limited data are available regarding unplanned VBAC, particularly in populations with restricted access to antenatal care (6, 11). It is rarely preferred by physicians due to the risk of serious complications such as uterine rupture, fetal demise, and postpartum hysterectomy (2). There is a prevailing concern that VBAC success rates decrease as the number of prior CS increases. However, the success rate of the procedure is approximately 75% in patients with two previous cesarean deliveries and a favorable pelvic outlet for vaginal birth. If these patients have a history of vaginal delivery, the risk of complications decreases to 1 in 4. Most physicians consider patients with two prior CS as potential candidates for VBAC, a view that is supported by the American College of Obstetricians and Gynecologists (ACOG) (12). Although there is limited information in the literature regarding patients with three prior CS, it has been emphasized that the success rate of the procedure is similar to that of patients with two prior CS (13). In our study, we observed a negative correlation, indicating that VBAC success decreased with an increasing number of CS. However, there were very few pregnant women with a history of more than one CS, which prevented us from performing a specific analysis for this subgroup.

Contrary to popular belief, birth intervals shorter than 24 months may increase the success of VBAC, whereas attempting VBAC within 18 months is associated with reduced success rates and an increased risk of complications (14). The success rate of VBAC was higher in patients with cervical dilatation greater than 3 cm at the time of admission and spontaneous rupture of membranes, compared to those who required labor induction (15). Durnwald et al. reported that VBAC success rates increase with higher Bishop scores (16). On the other hand, Helsel et al. reported that cervical dilatation is a more sensitive predictor of VBAC success than the Bishop score (17). The VBAC success rate in our study supports the findings of Kalok and Henselin, considering that all patients presented to the delivery room with cervical dilatation of at least 4 cm.

It has been stated that the most reliable predictive factor for VBAC success is a history of previous vaginal birth or prior successful VBAC. The success rate of VBAC in women with a history of vaginal birth (86.6%) is higher than in those without such a history (60.9%) (14). Indeed, considering the patients in our study for whom VBAC was not successful (7.4%), it can be stated that a history of vaginal delivery is an important predictive parameter. This is supported by the fact that 78.4% of the patients who underwent successful VBAC had a history of previous vaginal delivery.

In studies evaluating cervical length (CL) via USG in relation to VBAC success, the mode of delivery was CS in 78% of patients with a CL greater than 41 mm, and in 100% of those with a CL greater than 45 mm. However, 84% of patients with a CL below 28 mm achieved vaginal birth(18). Due to the design of our study, most patients presented with spontaneous labor and complete cervical dilatation, which limited our ability to perform statistical analysis regarding CL measurement.

Many studies have emphasized that the success rate of VBAC is below 50% when the estimated fetal weight exceeds 4000 g, and that the risk of uterine rupture increases if the pregnant woman has no history of vaginal delivery (19). In addition, Eden et al. reported that the likelihood of VBAC success decreases as gestational age increases, particularly beyond 41 weeks (20). In our study, the fact that the mean birth weight was 3024 g, the mean gestational age was 37 weeks, and that most patients (72.6%) had a history of vaginal delivery contributed to the high VBAC success rate.

The most frequently observed outcome among patients planned for VBAC was that those who were unable to deliver vaginally ultimately required a CS (17). We believe that this necessity may be attributed to physicians' medico-legal concerns arising from fetal distress and prolonged labor. The fact that all patients in our study who converted from VBAC to CS due to non-progressive labor and fetal distress were Turkish citizens supports this interpretation.

The risk of intrapartum uterine rupture increases in women with a lower uterine segment thickness less than 2 mm. The probability of uterine rupture during spontaneous vaginal birth after a Kerr incision is approximately 0.4% (19). Induction of labor in VBAC candidates and the use of prostaglandins as cervical ripening agents have been associated with an increased risk of uterine rupture. Studies on the use of mechanical dilators in VBAC are limited and report conflicting results (12). Low-dose oxytocin and balloon dilators can be used in selected VBAC cases. In our study, no method of labor induction other than amniotomy was performed in any patient, including those with myometrial thickness less than 2 mm. In this context, amniotomy appears to play a critical role in increasing the success of VBAC, as it contributes to the acceleration of labor.

In current studies, the maternal mortality rate associated with uterine rupture is reported to be around 1%, while the perinatal mortality rate is approximately 50%. Grünebaum et al. also reported significant neonatal morbidities in cases of planned home vaginal birth after CS (21), We agree with the view that VBAC should only be attempted when the necessary conditions for performing an emergency CS are in place (22). However, in another study by Assmani et al., it was emphasized that unplanned VBAC during spontaneous labor is associated with a higher birth success rate and a lower incidence of procedure-related complications, such as uterine rupture (23). In our study, while the VBAC success rate was 92.6%, the complication rate was 9.5%. In light of the literature, we believe that attempting unplanned VBAC in patients who meet these criteria may increase the success of the procedure while reducing complication rates. Patients presenting with cervical dilatation greater than 4 cm and/or ruptured membranes should be admitted to the clinic for delivery. Those who do not meet these conditions may be considered for home follow-up.

Many studies have shown that the mode of delivery may vary depending on patients' ethnic and cultural characteristics (14, 24). The vast majority of patients in our study were Syrian nationals, and most underwent VBAC without complications. We believe that this finding may be related to cross-cultural preferences for vaginal birth, as the primary CS rate among Syrian patients was significantly lower (6.3%) compared to Turkish patients during the 6-year study period.

Especially in cases where CS were performed abroad, the type of previous uterine incision was often unknown. This made the decision to proceed with VBAC more difficult and potentially risky. In the past, the Royal College of Obstetricians and Gynaecologists (RCOG) did not consider VBAC safe in patients with an unknown incision type. However, current guidelines emphasize that VBAC success rates are comparable in patients with both known and unknown incision types (14). Considering that Syrian refugee patients in this situation successfully underwent VBAC in our study, we support the current recommendation of the RCOG.

In addition, in support of our findings, a recently developed prediction model by Grobman et al. aimed to estimate VBAC success. In this model, race and ethnicity were excluded, and only variables known at the time of presentation—such as cervical dilatation, fetal position, and gestational age—were assessed. This study underscores the importance of clinical data in guiding Trial of Labor After Cesarean section (TOLAC) decisions and is consistent with our findings on unplanned VBAC outcomes(25).

According to our literature review, the fact that this is the first study to examine the outcomes of unplanned VBAC among Turkish and Syrian citizens in Türkiye constitutes an important strength. However, some limitations should be acknowledged. These include the relatively small sample size and the inability to perform multivariate statistical analyses due to missing data in certain clinical parameters. Consequently, the relationships between clinical characteristics and VBAC outcomes should be interpreted with caution. Future prospective studies with larger samples and

standardized data collection protocols will better elucidate the independent determinants of unplanned VBAC.

CONCLUSION

This study suggests that patients who have had a previous CS and are admitted to the delivery room in the active phase of labor may be a suitable population for VBAC. If desired by the patient, and if the necessary clinical infrastructure is available, vaginal delivery can be performed with close monitoring in this population.

Conflict of Interest: The authors declare no conflict of interest.

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Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Neset Gumusburun and Ulya Uskent. The first draft of the manuscript was written by Neset Gumusburun and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Investigation of the Relationship Between Serum Retinol-Binding Protein 4 Levels and Insulin Resistance, Homocysteine, and CRP Levels in Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Hastalarda Serum Retinol Bağlayıcı Protein 4 Seviyeleri ile İnsülin Direnci, Homosistein ve CRP Düzeyleri Arasındaki İlişkinin Araştırılması

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ABSTRACT

Aim: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive-age women, characterized by anovulation, hyperandrogenism, and menstrual irregularities. Its prevalence is approximately 6–8%, and insulin resistance is observed in 30–70% of affected individuals. Retinol-binding protein 4 (RBP4), a newly identified adipokine and specific carrier of vitamin A, has been shown to increase in insulin-resistant states. This study aimed to investigate serum RBP4 levels in women with PCOS and evaluate their association with metabolic parameters.

Materials and Methods: The study included 45 patients with PCOS and 45 healthy controls from Dr. Zekai Tahir Burak Training and Research Hospital. Fasting blood samples were collected and stored at -80 °C. Serum RBP4 levels were measured using the Enzyme-Linked Immunosorbent Assay (ELISA). Statistical analyses were performed using SPSS.

Results: No statistically significant difference in serum RBP4 levels was found between the two groups. However, HOMA-IR, androstenedione, total testosterone levels, LH/FSH ratio, and Ferriman-Gallwey Hirsutism Score were significantly higher in the PCOS group. HDL cholesterol levels were significantly lower in the PCOS group.

Conclusion: Our data suggest that RBP4 is not significantly associated with metabolic parameters such as insulin resistance and lipid profile in patients with PCOS. Therefore, the utility of RBP4 as an independent biomarker in the metabolic risk assessment of PCOS is limited. Further studies with larger sample sizes and prospective designs are needed.

Keywords: Polycystic ovary syndrome (PCOS); Retinol-binding protein 4 (RBP4); Insulin resistance; Homocysteine; C-reactive protein (CRP)

ÖZ

Amaç: Polikistik over sendromu; anovulasyon, amenore, adet düzensizliği ve hirsutizm gibi birçok klinik bulgusu olan, reprodüktif dönem kadınlarda en sık görülen endokrinopatidir. Toplumda prevalansı %6-8 dir. PKOS'lu kadınların büyük bir kısmında (%30–70) insülin rezistansına rastlanmaktadır. Retinol-bağlayacı protein 4 (RBP4) karaciğerden üretilen ve vitamin A için tek spesifik taşıyıcı protein olarak bilinen yeni keşfedilen bir adipokindir. RBP4 birçok insülin rezistanslı fare modellerinde seviyesi artan, adipositlerden salgılanan hormon olarak yayınlamıştır. Biz de çalışmamızda bir insülin rezistans durumu olan PKOS'lu kadınlarda serum RBP4 seviyelerini araştırdık.

Gereç ve Yöntemler: Çalışmamıza, Dr. Zekai Tahir Burak Eğitim ve Araştırma Hastanesi Jinekoloji polikliniğine başvuran PKOS tanısı konulan 45 hasta dahil edildi. Kontrol grubuna ise 45 sağlıklı kadın dahil edildi.Açlık serum RBP4 seviyeleri ölçümü için alınan örnekler serumları ayrılarak –80 derecede saklandı. Serum RBP4 seviyeleri ölçümü için tüm serumlar aynı anda 'Enzyme-Linked Immunosorbent Assay' (ELISA) yöntemi ile çalışıldı. Verilerin analizi SPSS for Windows programında yapıldı.

Bulgular: Serum RBP4 seviyeleri için iki grup arasında istatistiksel anlamlı farklılık saptanmadı. PKOS grubunun HOMA-IR, androstenedion, total testosteron düzeyleri ve LH/FSH oranları, Ferriman-Gallwey Hirsutizm Skoru anlamlı olarak yüksek bulundu. HDL Kolesterol seviyeleri ise PKOS grubunda anlamlı olarak daha düşük bulundu.

Sonuç: Çalışma verilerimizin sonuçlarına göre; RBP4'ün PKOS'lu hastalarda glukoz metabolizmasında ve insülin rezistansında henüz kullanılabilir bir marker olmadığını düşünmekteyiz. Bu testlerin klinikte kullanımı ve yüksek riskli grupların belirlenebilmesi için daha fazla sayıda çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Polikistik Over Sendromu (PCOS); Retinol-bağlayıcı protein 4 (RBP4); Insulin Direnci; Homosistein; C-reaktif protein (CRP)

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age, characterized by clinical findings such as anovulation, amenorrhea, menstrual irregularities, and hirsutism. Its prevalence varies between 6-8% depending on different diagnostic criteria. A significant proportion of women with PCOS (30-70%) exhibit insulin resistance (1).

Retinol-binding protein 4 (RBP4) is an adipokine produced by the liver and known as the specific carrier protein for vitamin A. Yang et al. reported that RBP4 is secreted by adipocytes and has increased levels in various insulin-resistant mouse models (2). Initially considered only as a retinol transporter, RBP4 has gained attention as an adipokine that may link GLUT4 expression in adipocytes to insulin resistance (3).

Animal studies have demonstrated a correlation between high RBP4 levels and reduced insulin sensitivity, body mass index (BMI), lipid profiles, and other metabolic syndrome components (2). However, human studies have yielded conflicting results (4,5).

In this study, we aimed to investigate serum RBP4 levels in women with PCOS, a condition associated with insulin resistance. Given that previous research has suggested an association between RBP4 and lipid metabolism, we also examined the correlation between serum RBP4 levels and lipid profiles. Additionally, we evaluated the relationship between serum RBP4 levels and µCRP, a marker of inflammation linked to obesity and insulin resistance, as well as homocysteine levels, which have been found to be elevated in some studies of PCOS patients.

Based on these findings, our objective was to determine whether RBP4 could serve as a potential biomarker for glucose and lipid metabolism in PCOS patients.

MATERIALS AND METHODS

This study was originally planned and conducted prospectively between 2008–2009 as a medical thesis at Zekai Tahir Burak Women's Health Training and Research Hospital. This study included 45 patients diagnosed with PCOS who visited the gynecology outpatient clinic at Dr. Zekai Tahir Burak Training and Research Hospital between January 2008 and June 2009. The diagnosis of PCOS was based on the revised Rotterdam criteria, requiring the presence of at least two of the following three features: oligo-anovulation (cycle length >45 days or fewer than six cycles per year), clinical or biochemical hyperandrogenism (Ferriman-Gallwey score >12 or serum testosterone levels above normal), and polycystic ovary morphology on transvaginal ultrasound (TV-USG).

Thyroid function tests, LH/FSH ratio, prolactin, 17-OHP, androstenedione, total and free testosterone levels were evaluated in all patients and controls. Patients with thyroid disease, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, or those who had used hormonal medications, ovulation induction agents, glucocorticoids, antiandrogens, or antihypertensive drugs in the past six months were excluded from the study. Women with comorbid conditions that could affect RBP4 levels were also excluded.

The control group consisted of 45 healthy women who attended the gynecology or family planning outpatient clinics during the same period. These women were clinically normal, normoovulatory, and were selected without considering body weight. All participants provided written informed consent after being fully informed about the study.

After detailed anamnesis, height and weight were recorded, and blood samples were collected from all participants during the early follicular phase (between days 3 and 5 of a spontaneous or progesterone-induced menstrual cycle). Venous blood samples were obtained from the forearm between 08:00 and 10:00 AM after 12 hours of fasting. Serum samples for fasting RBP4 levels were separated and stored at -80°C until analysis. Serum RBP4 levels were measured simultaneously using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated using the formula: HOMA-IR = (fasting insulin × fasting glucose (mg/dL)) / 450. Hirsutism was evaluated using the Ferriman-Gallwey scoring system. The study population was matched for age and BMI before being divided into two groups. The first group consisted of 45 patients diagnosed with PCOS, while the second group included 45 healthy control subjects.

Sample Size and Randomization

The sample size was determined based on an a priori power analysis, considering the expected effect size for differences in serum RBP4 levels and the capacity of the ELISA kit used. It was estimated that at least 40 participants per group would be required to achieve 80% power at a 5% significance level, and the planned sample size was deemed sufficient and feasible for the thesis study. Due to the observational nature of the study, no randomization was applied. Eligible patients were consecutively enrolled according to predefined inclusion and exclusion criteria.

Statistical Analysis

Data analysis was performed using SPSS. The Shapiro-Wilk test

was used to determine whether continuous variables were normally distributed. Comparisons between groups were made using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Correlations between continuous variables were evaluated using Spearman's correlation test. A p-value of <0.05 was considered statistically significant.

The study was conducted prospectively as a medical thesis at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008–2009, and ethics approval for publication was subsequently obtained from Ankara Bilkent City Hospital, which continues the mission of the former institution. This approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (Approval Date: 04.06.2025, Approval No: TABED 1/1350/2025) and the study was conducted in accordance with the Declaration of Helsinki and relevant national ethical standards.

RESULTS

The study population consisted of two groups: Group 1 included 45 patients diagnosed with PCOS, and Group 2 consisted of 45 normoovulatory healthy women. There was no statistically significant difference between the PCOS and control groups in terms of age and BMI (Table 1). Serum RBP4, homocysteine, and µCRP levels were not significantly different between the two groups (Table 1). However, the PCOS group had significantly higher HOMA-IR, androstenedione, total testosterone levels, and LH/FSH ratios compared to the control group. No significant differences were found between the two groups in terms of serum prolactin and 17-OH progesterone levels. However, the Ferriman-Gallwey hirsutism score was significantly higher in the PCOS group (Table 1).

Total cholesterol, LDL cholesterol, and triglyceride levels were higher in the PCOS group, but the differences were not statistically significant. However, HDL cholesterol levels were significantly lower in the PCOS group compared to the control group (Table 1).

The correlation analysis between serum RBP4 levels and HOMA-IR, homocysteine, µCRP, and total cholesterol levels was also examined. No significant correlation was found between serum RBP4 levels and these metabolic parameters in the overall study population, as well as in the PCOS and control groups separately (Table 2).

DISCUSSION

In current literature, the terms insulin resistance syndrome (IRS) and PCOS are often used interchangeably, leading to the assumption that they are closely related. However, insulin resistance cannot be demonstrated in up to 50% of obese PCOS patients using invasive tests, and this prevalence is even higher in non-obese patients (6,7). These findings indicate that PCOS and insulin resistance syndrome are not entirely equivalent. Women with PCOS exhibit impaired glucose utilization in peripheral tissues (8). In our study, we found significantly increased HOMA-IR levels in the PCOS group. Insulin resistance and related syndromes are independent risk factors for

Table 1. Demographic and Biochemical Measurements of PCOS and Control Groups

Variables	Group I (n = 45)	Group II (n = 45)	p-value
Age (years)	27.1 ± 4.2 (19–39)	28.5 ± 4.7 (18–39)	0.134
BMI (kg/m²)	25.2 ± 4.7	26.2 ± 6.0	0.393
RBP4 (ng/mL)	53.05 (16.46–165.00)	52.48 (19.92–165.00)	0.881
HOMA-IR	1.71 (0.40–6.17)	0.91 (0.31–3.39)	**<0.001***
Homocysteine (µmol/L)	8.67 (4.50–14.20)	7.81 (4.20–14.40)	0.223
Hirsutism Score (F-G)	15.14 ± 3.68	8.04 ± 1.85	**<0.001***
CRP (mg/L)	2.91 (0.13–14.56)	1.93 (0.17–15.26)	0.253
Androstenedione (ng/mL)	2.35 (0.15–5.07)	1.60 (0.85–3.70)	**<0.001***
Total Testosterone (ng/mL)	0.53 (0.17–1.38)	0.24 (0.04–0.51)	**<0.001***
LH/FSH Ratio	1.31 (0.44–4.22)	0.76 (0.23–2.47)	**<0.001***
Total Cholesterol (mg/dL)	172.4 ± 26.84	171.0 ± 30.64	0.813
Triglyceride (mg/dL)	105.0 (42.0–213.0)	78.0 (43.0–268.0)	0.092
LDL Cholesterol (mg/dL)	99.7 ± 22.87	91.0 ± 25.09	0.089
HDL Cholesterol (mg/dL)	50.8 ± 11.98	60.0 ± 13.57	**<0.001***
Prolactin (ng/mL)	13.92 ± 4.60	15.59 ± 4.62	0.650
17-OH Progesterone (ng/mL)	1.17 ± 0.47	1.24 ± 0.48	0.720

Student's t-test[1] was used for normally distributed variables (Age, BMI, Total Cholesterol, LDL, HDL, Prolactin, 17-OH Progesterone), while the Mann-Whitney U[2] test was used for non-normally distributed variables (other parameters). A p-value of <0.05 was considered statistically significant.
Abbreviations: PCOS: Polycystic Ovary Syndrome, BMI: Body Mass Index , RBP4: Retinol Binding Protein 4, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, µCRP: Micro C-Reactive Protein, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

Table 2. Correlation Between RBP4 Levels and Other Metabolic Parameters

Groups	HOMA-IR (r, p)	Homocysteine (r, p)	µCRP (r, p)	Total Cholesterol (r, p)	Triglycerides (r, p)
All Subjects RBP4 Levels	0.004, 0.968	0.033, 0.771	0.139, 0.223	0.134, 0.207	-0.015, 0.890
Group 1 (PCOS) RBP4 Levels	-0.005, 0.977	0.150, 0.330	0.215, 0.208	0.010, 0.950	-0.132, 0.388
Group 2 (Control) RBP4 Levels	0.007, 0.962	-0.092, 0.586	0.101, 0.519	0.227, 0.134	0.080, 0.600

Spearman's rank correlation test was used for analysis. A Bonferroni correction was applied, and a p-value <0.025 was considered statistically significant.
Abbreviations: PCOS: Polycystic Ovary Syndrome, RBP4: Retinol Binding Protein 4, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, µCRP: Micro C-Reactive Protein

cardiovascular disease, diabetes, hypertension, nephropathy, and dyslipidemia. These metabolic syndrome components may also be associated with elevated homocysteine levels in the long term. Sills et al. reported no statistically significant difference in plasma homocysteine levels between women with normal and polycystic ovaries (9). Similarly, in our study, there was no statistically significant difference in homocysteine levels between BMI- and age-matched PCOS and control groups. The differences in results among studies may be due to genetic, nutritional, and metabolic variations in the study populations.

Markers of chronic inflammation, such as µCRP, have been shown to be significant predictors of type 2 diabetes. Möhlig et al. found elevated µCRP levels in PCOS patients and suggested that the increased diabetes risk in PCOS may be related to chronic inflammation. In their study, µCRP levels were particularly high in obese PCOS patients (10). However, in our study, there was no significant difference in µCRP levels between BMI- and age-matched PCOS and control groups, which may be attributed to the similarity in BMI between the two groups.

The prevalence of abnormal lipid profiles in women with PCOS is approximately 70% according to the National Cholesterol Education Program Guidelines. Insulin resistance and compensatory hyperinsulinemia are often associated with decreased HDL cholesterol levels and increased total cholesterol, LDL, and triglyceride levels. Several studies have reported similar lipid profile abnormalities in PCOS patients (11,12). In our study, HDL cholesterol levels were significantly lower in the PCOS group compared to the control group, whereas no significant differences were found in triglyceride, total cholesterol, or LDL cholesterol levels between the two groups.

Recent animal studies have provided strong evidence for the relationship between insulin resistance and RBP4 levels. Insulin-resistant mice have elevated RBP4 levels in adipose tissue and serum, which can be normalized with insulin-sensitizing agents. Increased RBP4 levels in mice induce insulin resistance, whereas decreased RBP4 levels improve insulin sensitivity (2). However, human studies on the relationship between insulin resistance and RBP4 levels have produced inconsistent results. Recent evidence further supports the involvement of RBP4 in insulin resistance and pancreatic β-cell dysfunction, highlighting its potential contribution to the pathogenesis of type 2 diabetes (13,14).

In our study, there was no significant difference in serum RBP4 levels between the PCOS and control groups. This finding is consistent with studies by Hutchison et al. and Tan et al., which found no difference in RBP4 levels between overweight PCOS patients and controls after adjusting for age and BMI (5,15). However, other studies have suggested that elevated serum RBP4 levels may act as a linking factor between adipose tissue and insulin resistance in PCOS patients. Hahn et al. reported increased serum RBP4 levels in obese PCOS women compared to controls and suggested that these elevated levels might contribute to impaired glucose metabolism (16).

Some studies have found a significant association between RBP4 levels and hypertriglyceridemia (17,18). However, in our study, we did not observe any correlation between RBP4 levels and triglyceride or total cholesterol levels, which is consistent with the findings of Choi et al. (19). Similarly, our study did not find a correlation between serum RBP4 levels and insulin resistance (HOMA-IR), which aligns with some recent studies (16,20). However, other studies have reported a positive correlation between serum RBP4 levels and insulin resistance (21,22), suggesting that high RBP4 levels are associated with reduced insulin clearance and negatively correlated with insulin secretion (23).

This study also had some limitations. The small sample size and the single-center design were major limitations.Additionally, variations in RBP4 test kits and laboratory procedures might have influenced

the measurement results. Confounding factors that could affect insulin resistance and RBP4 levels, including dietary habits, physical activity levels,and genetic polymorphisms, were not evaluated.

Future prospective studies with larger, multi-center cohorts and a more comprehensive assessment of potential confounding factors are needed to better understand the role of RBP4.

CONCLUSION

Based on our findings, serum RBP4 levels do not appear to be significantly associated with metabolic parameters such as insulin resistance and lipid profile in patients with PCOS. Therefore, the utility of RBP4 as an independent biomarker for metabolic risk assessment in PCOS is limited. Further studies with larger sample sizes and prospective designs are needed to better clarify its potential clinical relevance.

Ethics Committee Approval: This approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (Approval Date: 04.06.2025, Approval No: TABED 1/1350/2025) and the study was conducted in accordance with the Declaration of Helsinki and relevant national ethical standards.

Conflict of Interest: The authors report no financial relationships relevant to this work.

Financial Disclosure: All authors have declared that they have no financial relationships.

Author Contributions: EB: Conception and design of the study, data collection, data analysis, and manuscript writing; HCG: Data interpretation, literature review, and critical revision of the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Investigation of the Effect of Granulocyte Colony-Stimulating Factor on Endometrial Thickness in the Wistar Albino Rat

Wistar Albino Sıçanında Granülosit Koloni Uyarıcı Faktörün Endometrial Kalınlık Üzerindeki Etkisinin Araştırılması

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ABSTRACT

Aim: A thin endometrium is a difficult situation for infertile patients and the doctors who treat them. In our study, we wanted to investigate the efficacy of G-CSF, which can be used for the treatment of infertile couples with thin endometrium, by examining the effect of GCSF on the endometrium in rats.

Material and Methods: In our study, which we used as an animal model, we divided 50 rats into five groups and investigated the effect of G-CSF on thin, rat endometriums obtained using alcohol. Endometrial and uterine thickness were performed semi-quantitatively by an impartial pathologist. At the end of the study, the rats' hemoglobin levels and weight were measured.

Results: When the pathological samples were examined, it was found that G-CSF increased the thickness of the endometrial surface epithelium at the dose and duration administered, but had no effect on the thickness of the uterus and endometrium. Weight and hemoglobin levels were lower in the groups of rats exposed to the surgical procedure than in the control group.

Conclusions: The effect of G-CSF on the endometrium is evaluated differently in various studies in the literature. The main reason for this is that studies on the thin endometrium are not physiopathologically standardized. In our study, we found that G-CSF increased the thickness of the endometrial surface epithelium. We believe that this promotes embryo implantation.

Keywords: Infertility, G-CSF, endometrium, rat

ÖZ

Amaç: İnce endometrium, infertil hastalar ve onları tedavi eden doktorlar için zorlu bir durumdur. Bu çalışmada, infertil çiftlerin tedavisinde kullanılabilecek olan G-CSF'nin etkinliğini araştırmak ve G-CSF'nin endometrium üzerindeki etkisini incelemek amacıyla bir hayvan modeli kullanarak çalışmamızı gerçekleştirdik.

Gereç ve Yöntemler: Hayvan modeli olarak kullandığımız bu çalışmada, 50 sıçan beş gruba ayrıldı ve alkol kullanılarak elde edilen ince endometriumlu sıçanlarda G-CSF'nin etkisi araştırıldı. Endometrial ve uterin kalınlık, tarafsız bir patolog tarafından yarı kantitatif olarak değerlendirildi. Çalışmanın sonunda sıçanların hemoglobin düzeyleri ve kiloları ölçüldü.

Bulgular: Patolojik örnekler incelendiğinde, uygulanan doz ve sürede G-CSF'nin endometrial yüzey epiteli kalınlığını artırdığı, ancak uterus ve endometrium kalınlığı üzerinde etkisinin olmadığı görüldü. Cerrahi işleme maruz kalan sıçan gruplarında kilo ve hemoglobin düzeylerinin kontrol grubuna göre daha düşük olduğu tespit edildi.

Sonuç: G-CSF'nin endometrium üzerindeki etkisi, literatürdeki farklı çalışmalarda farklı şekilde değerlendirilmiştir. Bunun başlıca nedeni, ince endometrium üzerine yapılan çalışmaların fizyopatolojik olarak standardize edilmemiş olmasıdır. Bizim çalışmamızda, G-CSF'nin endometrial yüzey epiteli kalınlığını artırdığı sonucuna ulaştık. Bunun embriyo implantasyonunu desteklediğine inanıyoruz.

Anahtar Kelimeler: İnfertilite, G-CSF, endometrium, sıçan

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INTRODUCTION

Worldwide, 15-20% of couples suffer from infertility. With advances in assisted reproduction and therapy, pregnancy rates have risen. In vitro fertilization (IVF) cycles require a healthy embryo, a successful treatment procedure and an endometrium appropriate for implantation.(1) Since a thin endometrium typically causes implantation failures and cycle cancellation, long-term estrogen therapy, vasoactive drugs and endometrial scraping have been used to thicken it. None of these techniques have consistently helped patients. Increased endometrial thickness and responsiveness was studied with immunotherapy. (2,3)

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein produced by bone marrow, stromal, mononuclear, fibroblast, natural killer and endometrial cells. G-CSF primarily stimulates the growth and differentiation of neutrophils in the bone marrow and controls their release into the bloodstream. Studies have examined its use in the treatment of couples with recurrent IVF failure.(4,5) G-CSF levels in follicular fluid are thought to influence ovulation and pregnancy.(6) G-CSF influences trophoblast development and placental metabolism, and trophoblast cells express the receptor. These data suggest that G-CSF affects the trophoblast, placenta and embryo implantation.(7) In this study, the effects of G-CSF on the thin endometrium and uterus were investigated in an animal model.

MATERIAL AND METHODS

The local ethics committee for animal experiments at Bülent Ecevit University approved our study (protocol no.: 2015-16-01/07). Fifty female Wistar albino rats weighing between 250 g and 280 g were obtained from the Bülent Ecevit College animal laboratory for our project. The experimental animals were divided into five groups and monitored daily to assess their estrous cycles, while cellular changes in the cervix uteri were analyzed microscopically by cervical smears. Using the Papanicolaou staining method, the predominant cell type (intermediate, basal, superficial, cornified epithelial cells, etc.), the relative abundance of leukocytes, the ratio of superficial cells to other epithelial cells, eosinophilic cytoplasm and nuclear shrinkage were examined to determine the phase of the estrous cycle.

- Experimental group 1: (alcohol+G-CSF) with endometrium thinned by intrauterine alcohol administration and s.c. G-CSF treated group.
- Experimental group 2: (alcohol + PSS) with endometrium thinned by intrauterine administration of alcohol and s.c. physiological saline solution (PSS) was injected.
- Experimental group 3: (G-CSF)The group in which only s.c. G-CSF was injected.
- Experimental group 4: (PSS) The group in which only s.c. physiological saline solution was injected.
- Experimental group 5: (Control) The group that did not undergo any surgical or medical intervention.

The alcohol+G-CSF group was formed to demonstrate the effect of G-CSF on thin endometrium; the alcohol+PSS group was formed to confirm the effect of G-CSF on thin endometrium; the G-CSF group was formed to demonstrate the effect of G-CSF on normal endometrium; the PSS group was formed to study the effect of stress induced by daily G-CSF injection on endometrium; the control group was formed to confirm the results of the other groups.

Iatrogenic Protocol for the Creation of a Thin Endometrium

The abdomen of the rat was inserted through a 2 cm incision in the lower ventral segment, with the timing chosen according to the determination of the phases of the estrous cycle. During the estrus phase, intraperitoneal anesthesia was administered with ketamine at a dose of 80-100 mg/kg and the area was then shaved and cleaned with povidone-iodine. The uterine horns were pulled out of the abdomen and ligated as close as possible to the ovaries with a silk 2-0 suture. At the level of the cervix, the uterus was clamped with a non-crushing clamp and 0.1 ml of 95% ethyl alcohol was injected into both horns while the filling of the horns was monitored. After a waiting period of 3 minutes, the injection of 0.1 ml was repeated in both horns and after a further waiting period of 2 minutes the cervical clamp was opened. The uterine horns were placed in the abdominal cavity, the muscle layer and the anterior abdominal wall were sutured with 2-0 polyglactin 910 and the skin of the rats was sutured with 2-0 silk. After the surgical procedure, the rats were monitored for 4-6 hours to wake up from anesthesia. All animals participating in the experiment were given commercial pellets (12-16 mm diameter) and water ad libitum in a 14-hour light/10-hour dark cycle in the Bülent Ecevit College animal laboratory.

Procedure for G-CSF Administration

The cycle phase was determined in the group in which a thin endometrium was applied after waiting for two–estrous cycles and in the other groups by observation in the following cycle. A subcutaneous G-CSF injection of 40 µg/kg/day was administered for 5 days from the first day of the estrous cycle. The G-CSF injection was continued for a total of 4 cycles and administered during the first 5 days of the estrous cycle.

A similar procedure was used in the PSS group as in the groups with G-CSF injections.

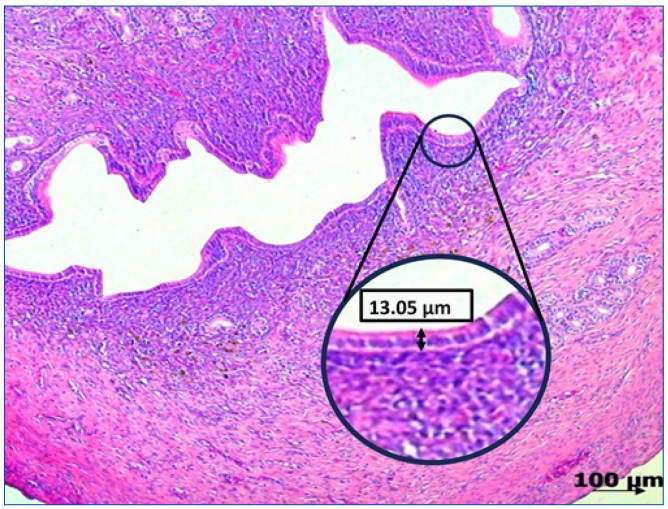
Measurement of the Hemoglobin Level and Body Weight of Rats

The weights of the rats, which had a homogeneous weight distribution before the experiment, were measured under anesthesia shortly before they were euthanized by hysterectomy and exsanguination. Blood samples obtained by exsanguination were evaluated in the microbiology laboratory of Bülent Ecevit College Health Application and Research Center using the CA USA brand Beckman Coulter Unicel DXH 800 Slidemarker Stainer for a complete blood count. Coulter DxH Cell Lysey, Coulter DxH Diff Pack, Coulter DxH Retic Pack and Coulter DxH Cleaner solutions were used in this evaluation.

Histopathological Examination Procedure

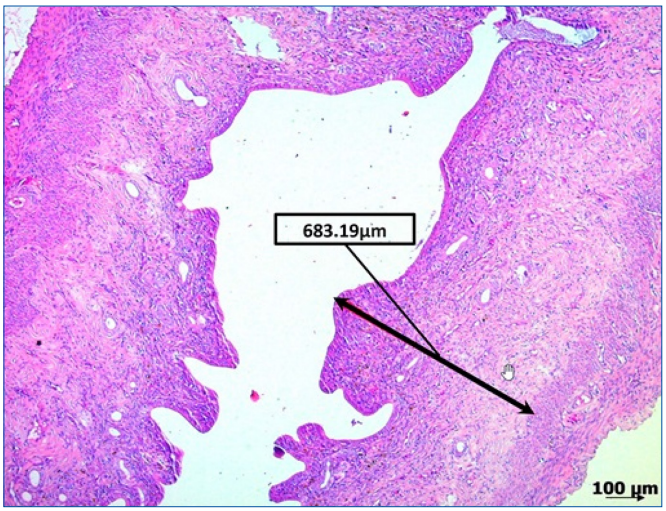
Hysterectomy was performed in rats in the estrus phase of the last cycle treated with G-CSF. The removed specimen was preserved in 10% formaldehyde solution and collected for histologic and pathologic examination. For histopathologic examination, the tissues were embedded in paraffin and hematoxylin-eosin (H&E) sections were prepared from these paraffin blocks. The H&E sections prepared for the uterus were analyzed by light microscopy (Leica DM2500 Optical Microscope Systems, Germany) by an impartial pathologist who did not know the groups. Microscopic images (Imaging System, Zeiss Microscope Axio Imager. A2m, U.S.) were obtained for each study group. The thickness of the endometrial surface epithelium, the thickness of the endometrium and the total thickness of the uterus were measured digitally semi-quantitatively. Considering the endometrial and total uterine thickness of all groups and the areas with the least epithelial indentations, 6 areas of each sample were determined and the average values were calculated by measuring these areas. (Figure 1-5) The pathological specimens were blinded for the pathologists.

Figure 1. Examples for measuring the thickness of the endometrial epithelium.



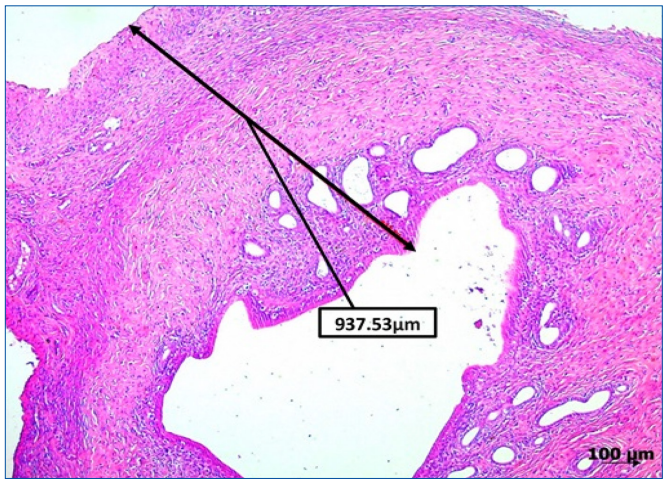
Experimental group 1: (alcohol+G-CSF) " " It shows the measurement of the epithelium thickness in the zoomed part within the circle.

Figure 2. Examples for measuring the thickness of the endometrium.



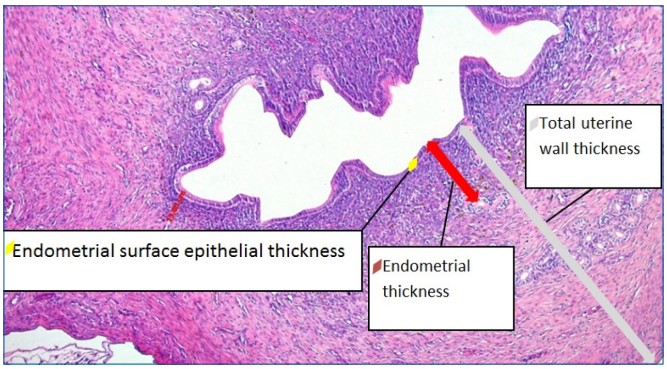
Experimental group 5: (Control) The black arrow shows the total thickness of the endometrium.

Figure 3. Examples for measuring the thickness of the uterus.



Experimental group 4: (PSS) The black arrow shows the total thickness of the uterus.

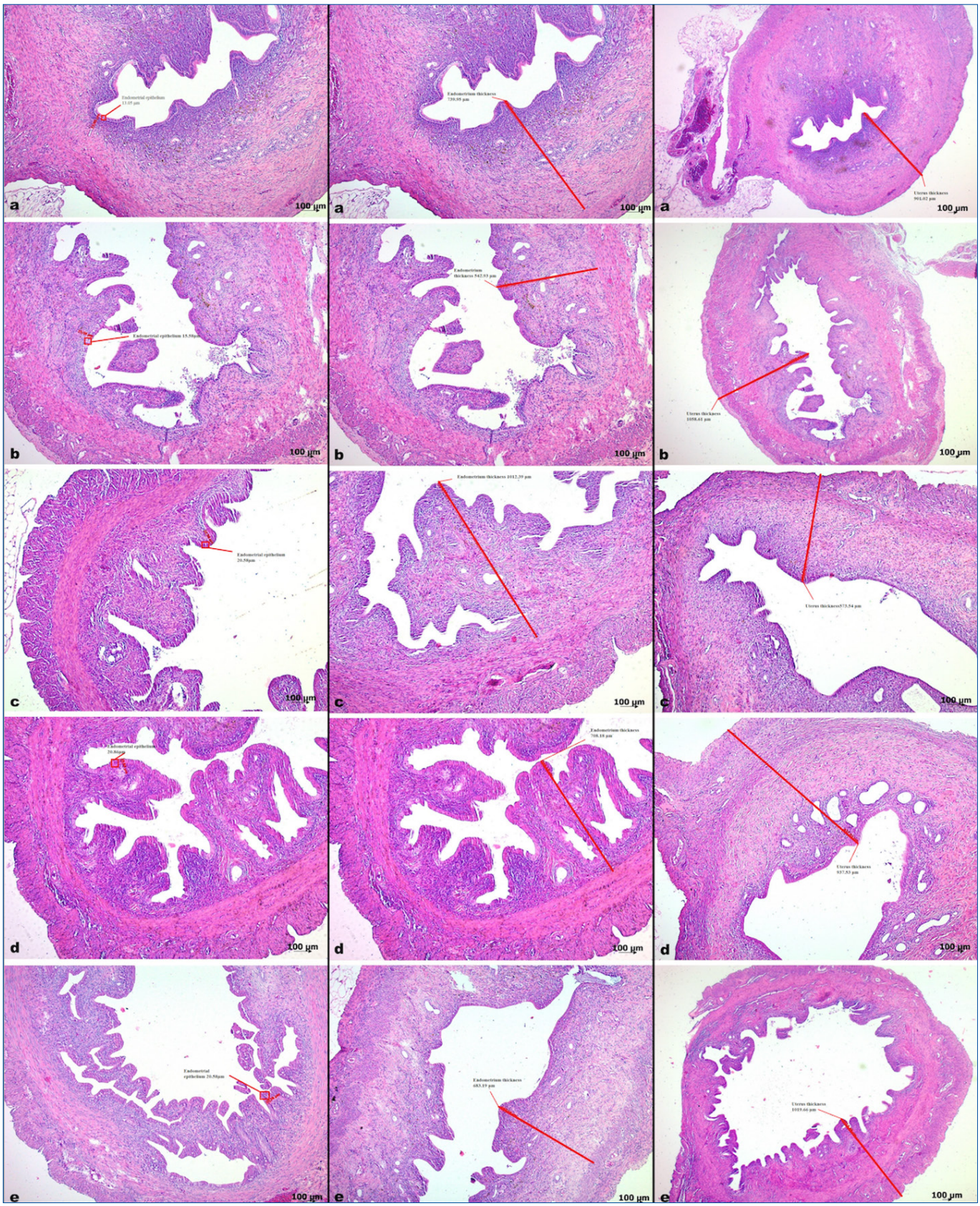
Figure 4. Examples for measuring the thicknesses.



Experimental group 1: (alcohol+G-CSF)

The yellow arrow shows the thickness of the surface epithelium of the endometrium; the red arrow shows the thickness of the endometrium; the gray arrow shows the total thickness of the uterine wall.

Figure 5. Endometria of the rats in the different groups



a: alcohol+G-CSF; b:alcohol+PSS; c:G-CSF; d:PSS; e: Control

This figure shows the measurement methods on similar or identical histological sections.

Table 1. Mean, standard deviation, median, minimum and maximum values for the thickness of the endometrial surface epithelium, the thickness of the endometrium and the total thickness of the uterine wall for each group.

Groups	Endometrial surface epithelial thickness (µm)	Endometrial thickness (µm)	Total uterine wall thickness (µm)
Alcohol + G-CSF (n=10) mean±SD median (min-max)	23.4±7.56 24.6 (11.6-32.6)	570±287.2 592 (238-855)	987±200.6 978 (773-1228)
Alcohol + PSS (n=9) mean±SD median (min-max)	10.6±3.24 9.1 (7.6-15.6)	711±157.9 765 (490-878)	1087±270.4 1067 (782-1412)
G-CSF (n=10) mean±SD median (min-max)	18.4±3.05 17.4 (15.3-23.4)	731±245.4 601 (526-1118)	1068±300.7 1088 (740-1472)
PSS (n=10) mean±SD median (min-max)	19.7±2.95 19.2 (15.6-24.9)	690±130.8 692 (540-869)	1105±168.9 1165 (851-1316)
Control (n=10) mean±SD median (min-max)	20.3±3.62 20.1 (15.6-26.1)	667±73.2 670 (542-746)	1021±135.9 1046 (797-1197)
Total (n=49) mean±SD median (min-max)	18.6±6.0 18.7 (7.6-32.6)	673±195.9 691 (238-1118)	1053±217.9 1061 (740-1472)
p- value	**<0.001**	0.803	0.751

G-CSF, granulocyte colony-stimulating factor ; PSS, physiological saline solution.

Table 2. p-values comparing the groups in terms of the thickness of the surface epithelium of the endometrium.

Groups	Alcohol + G-CSF	Alcohol + PSS	G-CSF	PSS	Control
Alcohol + G-CSF		**0.001**	0.750	0.105	0.393
Alcohol + PSS	**0.001**		**0.001**	**<0.001**	**<0.001**
G-CSF	0.750	**<0.001**		0.315	0.190
PSS	0.105	**<0.001**	0.315		0.684
Control	0.393	**<0.001**	<0.190	0.684	

G-CSF, granulocyte colony-stimulating factor ; PSS, physiological saline solution. Statistically significant p-values are in bold.

Monitoring postoperative well-being: Postoperative welfare monitoring and follow-up of the rats participating in the study were conducted according to the recommendations of the Institutional Animal Care and Use Committee (IACUC). For rats undergoing midline incision surgery, daily postoperative monitoring was performed for the first 7-10 days (including weekends and holidays). This monitoring was performed simultaneously by the study investigators and the veterinarian of the Bülent Ecevit College Animal Experimentation Laboratory . The areas of surgical incisions, diet, body temperature and water intake of the rats were monitored. The rats were not given analgesic or prophylactic antibiotic treatment so as not to cause a reaction with G-CSF, which was the subject of the animal experiment, or to affect the elimination process of the drug. Since the suturing of the midline incision was performed with absorbable suture material, it was not necessary to remove the sutures later. No lethargy, loss of appetite, fever, wound dehiscence, signs of infection (redness, excessive swelling or discharge), missing suture material or wound dehiscence were observed at the controls.

Table 3. Mean, standard deviation, median, minimum and maximum values for weight, hemoglobin for each group.

Groups	Weight (gr)	Hb (g/dl)
Alcohol + G-CSF (n=10) mean±SD median (min-max)	247±24.9 249 (210-280)	12.2±0.5 12.0 (11.5-13.0)
Alcohol + PSS (n=9) mean±SD median (min-max)	249±11.4 248 (231-269)	12.5±1.4 12.3 (10.9-14.4)
G-CSF (n=10) mean±SD median (min-max)	266±16.4 260 (249-295)	14.2±1.1 14.5 (12.5-15.2)
PSS (n=10) mean±SD median (min-max)	249±14.6 258 (249-274)	13.7±0.9 13.6 12.2-14.9
Control (n=9) mean±SD median (min-max)	274±9.1 274 (263-286)	13.8±0.9 13.4 (12.8-14.9)
Total (n=48) mean±SD median (min-max)	257±19.0 258 (210-295)	13.3±1.3 12.9 (10.9-15.9)
p-value	**<0.001**	**<0.001**

Hb, hemoglobin; WBC, white blood count; G-CSF, granulocyte colony-stimulating factor ; PSS, physiological saline solution.

Table 4. p-values comparing the groups in terms of weight, hemoglobin, white blood count, neutrophils.

	Alcohol + G-CSF	Alcohol + PSS	G-CSF	PSS	Control
WEIGHT					
Alcohol + G-CSF		0.971	0.165	1.000	**0.006**
Alcohol + PSS	0.971		**0.009**	0.971	**0.001**
G-CSF	0.165	0.009		**0.019**	0.095
PSS	1.000	0.971	**0.019**		**0.001**
Control	**0.006**	**0.001**	0.095	**0.001**	
HEMOGLOBIN					
Alcohol + G-CSF		0.661	**0.001**	**0.002**	**<0.001**
Alcohol + PSS	0.661		**0.002**	0.095	**0.024**
G-CSF	**0.001**	**0.002**		0.353	0.604
PSS	**0.002**	0.095	0.353		0.604
Control	**<0.001**	**0.024**	0.604	0.604	

G-CSF, granulocyte colony-stimulating factor ; PSS, physiological saline solution. Statistically significant p-values are in bold.

Statistical Analysis

The statistical analysis was performed with the program SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as arithmetic mean±standard deviation and median (minimum-maximum). Kruskal-Wallis analysis of variance was used to compare the groups. In the Kruskal-Wallis analysis of variance, the pairwise comparison of the subgroups was carried out using the Dunn test. For all evaluations, the p-value < 0.05 was considered significant. The groups were blinded for the statisticians.

RESULTS

Of the 50 subjects enrolled in the study, which were randomly divided into five groups according to age and body weight, one rat in the alcohol + PSS group was considered unsuitable for histopathologic examination and blood count evaluation due to an intra-abdominal infection. One rat in the control group was excluded from the blood count analysis because the blood sample had clotted prior to analysis.

There was no statistically significant difference between the groups with regard to the total thickness of the uterine wall and the endometrium. When evaluating the thickness of the endometrial surface epithelium, the alcohol + PSS group had the lowest value compared to the other groups. ($p < 0.005$) (Table 1) There was no statistically significant difference between the other groups in terms of endometrial surface epithelium. ($p > 0.05$) (Table 2)

At the end of the study, the group with the highest weight in the weight measurements taken shortly before the rats were euthanized by exsanguination was the control group. The alcohol+PSS group had the lowest median weight. Compared to the control group, the median and mean values were lower in the alcohol+G-CSF, alcohol+PSS and PSS groups. ($p < 0.001$) Hemoglobin levels were statistically significantly lower in the groups exposed to the surgical intervention (alcohol + G-CSF and alcohol + PSS) than in the control group. ($p < 0.001$; $p=0.024$) The lowest hemoglobin level was found in the alcohol + G-CSF group. The G-CSF group had the highest hemoglobin level. (Table 3) The p-values for the pairwise comparisons of the groups in terms of weight and hemoglobin are shown in Table 4.

DISCUSSION

There are numerous studies in the literature on the effects of a thin endometrium on infertility and its treatment. Some of these relate to drug treatment and others to the receptivity of the endometrium. In any case, a thin endometrium and its treatment is a challenge. Multiple studies consistently demonstrate a correlation between a thin endometrium and unfavorable outcomes in the process of implantation. (8-10) Thin endometrium is difficult to treat and attempts are made to increase the pregnancy and implantation rate. Various treatment methods (low-dose acetylsalicylic acid, estrogen replacement, vitamin E, etc.) have been tried in the literature. Various etiopathogeneses have been investigated and treated in studies. In the past, vitamin E, sildenafil and acetylsalicylic acid were the most prominent among the studies in which the effects of various medications and dietary supplements on the thin endometrium were investigated. (11) It has been shown that the use of pentoxifylline and tocopherol in thin endometrium leads to positive pregnancy results and improves the pregnancy rate. (12) There is evidence that vaginal sildenafil improves uterine artery blood flow and endometrial development in IVF patients with previously poor endometrial response. (13) In addition, Ikoma T and

colleagues have shown that bone marrow cells transplanted from male donors were detected by immunofluorescence labeling of the Y chromosome in endometrial curettage pathologies from female patients. This suggests that bone marrow-derived stem cells may be a source of endometrial stem cells and that G-CSF may have an effect on the endometrium via this mechanism. (14) Although these similar studies have inspired many new studies, they suggest that the agents used act on the thin endometrium via hypothetical pathways, as they do not define a clear pathophysiological pathway for the cause of the thin endometrium and patients are not standardized in this way. To avoid this situation, we believe that a study investigating the effect of a single agent on the thin endometrium, standardized in the same way, will provide more accurate results. In our study planned for these reasons, we found that G-CSF increased the thickness of the endometrial epithelium. There was no significant difference in endometrial epithelial thickness between the alcohol+G-CSF group and the control, PSS and G-CSF groups, but higher values of epithelial thickness in the alcohol+G-CSF group than in the alcohol+PPS group. This shows that G-CSF increases the epithelial thickness of the endometrium. The observation of the lowest endometrial epithelial thickness in the alcohol + PSS group among the study groups showed that the method was successful in producing a thin endometrium epithelium. The fact that only the G-CSF-treated group showed no significant difference from the control group and the PSS group in terms of endometrial epithelial thickness indicates that G-CSF has no significant effect on rats whose endomerium is not thin. Since we assume that the effect of G-CSF in the studies mentioned is directed at the surface epithelium of the endometrium, we think that the treatments with medical agents (VEGF, sildenafil, etc.) have indirect effects. In this context, it appears that only the right indication for the use of G-CSF will lead to successful treatment. In the PSS group, which was exposed to a daily injection, it was shown that the daily injection stress had no influence on the thickness of the endometrial epithelium, which did not differ from the control group. The fact that there was no difference between the groups in terms of total uterine thickness and total endometrial thickness suggests that the effect of G-CSF on these parameters is not significant. Fatemeh Sarvi and colleagues found that using GCFS in women with thin endometrium on HCG injection, oocyte retrieval, and embryo transfer increased endometrial thickness and implantation rate. (15) Maryam Eftekhar et al. observed that G-CSF may thicken endometrium. It has not been found to increase chemical and clinical pregnancy rates in infertile women with thin endometrium in frozen embryo transfer. This may be because G-CSF (Leukemia Inhibitory Factor) promotes LIF and reduces CD16, CD56, which are crucial to implantation. (16) In the study by Won et al. on the best time of intrauterine GCSF injection and its effects on the endometrium, adhesion molecules increased and natural killer cell activity decreased. (17) All these results are indeed related to the surface epithelium of the endometrium, the importance of which was emphasized in our study.

G-CSF can be synthesized by multiple cells at the maternal-fetal interface and contributes to the regulation of trophoblast development, endometrial decidualization, placental metabolism and angiogenesis. It is an important means of intercellular communication. The study by Jinli Ding and colleagues showed that G-CSF from M2 macrophages can promote trophoblast invasion and migration by activating the PI3K/AKT/Erk1/2 signaling pathway and thus may be involved in the normal course of pregnancy. (18) Combining the results of these studies with the results of our study, we believe that the success of implantation is achieved by increasing the thickness of the endometrial epithelium where the embryo's first point of contact with the mother, and that this is related to adhesion molecules and inflammatory processes. We believe that the discrepancy between chemical pregnancy and clinical pregnancy rates between studies is due to the lack of standardization of the physiopathology of the thin endometrium. In these studies, when investigating the effects of G-CSF on the thin endometrium, the part of the endometrium on which it mainly has a morphological effect should be considered.

The meta-analysis of 14804 individuals from 20 research between 2014 and 2022 found that in vitro fertilization in patients with endometrial receptivity problems is not only dependent on endometrium state. The comprehensive analysis found that women with endometrial receptive dysfunction need a tailored strategy with high-quality diagnostic and successful therapy to attain appropriate thickness and enhanced endometrial receptivity. Due to methodological flaws in the included studies, more study is needed to determine endometrial thickness, structure, treatment procedures, and other parameters' independent value. (19) G-CSF improves endometrial receptivity and conception rates, according to 10 research from 2011 to 2017 that included 475 individuals. The research is conflicting and hard to compare due to the small number of studies on this issue and the diverse study styles. More controlled, randomized studies with more people are needed to identify the right prescription, dosage, and duration. (20) The common point of these meta-analyses is that a thin endometrium has different outcomes in implantation, biochemical pregnancy, clinical pregnancy and live birth rate and that further studies are needed. Furthermore, as shown in studies examining the relationship between infertility and the endometrium, many molecular factors and demographic changes are influential. (21) We believe that the reason for this is that the physiopathology of thin endometrium is not clearly understood. In our study, we have shown that G-CSF increases epithelial surface epithelium thickness

in thin endometrium obtained by the same method (cytotoxic alcohol). However, we think that it may also be useful in women with similar causes such as Asherman's syndrome or previous endometritis. We can also imagine that G-CSF contributes to the success of implantation and IVF by increasing the receptivity of the endometrium due to the enlarged surface epithelium.

Looking at weight and postoperative hemoglobin levels, which are the secondary outcomes of the study, the highest body weight is seen in the control group which was not exposed to any intervention. The fact that the G-CSF group has a higher body weight on average than the PSS group and there is no statistically significant difference between it and the control group shows that the G-CSF group has no effect on weight loss. The fact that there is no statistically significant difference in postoperative hemoglobin in the G-CSF group compared to the control and PSS groups shows that G-CSF is not a risk factor for anemia. The hemoglobin levels in the alcohol+G-CSF and alcohol+PSS groups exposed to the surgical procedure are statistically significantly lower than in the control group. The postoperative hemoglobin level in the G-CSF group does not differ from that of the PSS group and the control group. For this reason, we believe that G-CSF has no negative effects on anemia.

Our animal model study, which was designed to shed light on treatment with G-CSF to increase endometrial thickness, differs from other studies on the effect of G-CSF in the relationship between drug dose, application method and time. Many studies on the same topic and more generally studies on the relationship between the endometrium and implantation, pregnancy rates and live birth rates show that there are many different factors in this cascade. Pathology occurring at any point in this cascade has an impact, from obtaining a suitable endometrium to embryo implantation and even live birth rates. With our study, in which we investigated the endometrial epithelium thickness aspect of this cascade, we aimed to contribute to the literature and demonstrate the histologic effects of G-CSF application on the endometrium. As this was an animal study, the physiopathology of the thin endometrium was standardized in our study and the effect of G-CSF was more clearly visible thanks to this standardization. We believe that we differed positively from other studies in this respect. Unfortunately, due to the nature of our study, the uterus of the rats was removed, so we could not determine the implantation and live birth rates after G-CSF application in rats.

CONCLUSION

Consequently, infertility due to a thin endometrium is a problem whose physiopathology and treatment is difficult. In this study, which can serve as a benchmark for the animal model we created and subsequent studies, we recommend clinicians and researchers to determine the cause of thin endometrium or plan treatment for the possible cause. We believe that not every infertility patient with thin endometrium can be treated with G-CSF and that randomized controlled trials are needed to develop the right treatment protocols for the right patient. Future studies on the treatment of infertility with a thin endometrium or G-CSF therapy should focus on the endometrial surface epithelium and aim to determine whether the increase in epithelial endometrial thickness induced by G-CSF treatment in thin endometrium is due to increased migration of bone marrow precursors with subsequent differentiation and maturation or due to G-CSF treatment-induced proliferation of epithelial cells. It should be noted that the effect of G-CSF is morphologically based on the surface epithelium of the endometrium. The effect of G-CSF on endometrial surface epithelium thickness has been demonstrated at the histopathological level, but its direct clinical implication for infertility treatments has not yet been clearly established.

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Ethics Statement: The study was approved by the Ethics Committee for Animal Experiments of Bülent Ecevit University with the assigned protocol number 2015-16-01/07.

Disclosure Statement: The authors have declared no potential conflict of interest.

Declaration of Competing Interest: The authors declare no potential conflicts of interest.

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Use of Inflammatory Markers in the Diagnosis of Ectopic Pregnancy

Enflamatuvar Belirteçlerin Ektopik Gebelik Tanısında Kullanımı

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ABSTRACT

Aim: This study aimed to evaluate the utility of inflammatory markers, including the systemic immune-inflammation index, systemic inflammatory response index, and pan-immune inflammatory value, in diagnosing ectopic pregnancy.

Material and Methods: A retrospective analysis was conducted on 105 patients diagnosed with ectopic pregnancy and 105 patients with intrauterine pregnancies treated at our hospital between November 2022 and September 2023. Ectopic pregnancy diagnoses were confirmed through ultrasonography. Data collected included age, gravida, parity, white blood cell count, neutrophil count, monocyte count, lymphocyte count, and platelet count. The inflammatory markers were calculated and compared between the groups using statistical software.

Results: Significant differences were observed in white blood cell, neutrophil, monocyte, and lymphocyte counts. The systemic immune-inflammation index values were significantly higher in the ectopic pregnancy group (890.70±545.30) compared to the intrauterine pregnancy group (1121.50±537.59, p=0.004). Similarly, the systemic inflammatory response index and pan-immune inflammatory value were significantly elevated in the ectopic pregnancy group (systemic inflammatory response index: 70.31±29.70 vs. 89.07±32.49, p=0.000; pan-immune inflammatory value: 477.56±270.08 vs. 679.77±319.18, p=0.000). Receiver operating characteristic curve analysis showed moderate diagnostic accuracy for these markers with area under the curve values of 0.670, 0.670, and 0.710, respectively.

Conclusions: Inflammatory markers such as the systemic immune-inflammation index, systemic inflammatory response index, and pan-immune inflammatory value show potential as diagnostic tools for ectopic pregnancy. Incorporating these markers into clinical practice could improve diagnostic accuracy, complementing traditional methods. Further research with larger sample sizes is required to validate these findings and enhance their clinical application.

Keywords: Ectopic pregnancy, biomarkers, inflammation, immune system

ÖZ

Amaç: Bu çalışmada, sistemik immün inflamasyon indeksi, sistemik inflamatuar yanıt indeksi ve pan-immün inflamatuar değer gibi inflamatuar belirteçlerin ektopik gebelik tanısında kullanılabilirliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Kasım 2022 ve Eylül 2023 tarihleri arasında hastanemizde tedavi edilen 105 ektopik gebelik tanılı hasta ve 105 intrauterin gebelik tanılı hasta üzerinde retrospektif bir analiz yapıldı. Ektopik gebelik tanıları ultrasonografi ile doğrulandı. Toplanan veriler arasında yaş, gravida, parite, lökosit sayısı, nötrofil sayısı, monosit sayısı, lenfosit sayısı ve trombosit sayısı yer aldı. İnflamatuvar belirteçler hesaplandı ve istatistiksel yazılım kullanılarak gruplar arasında karşılaştırıldı.

Bulgular: Lökosit, nötrofil, monosit ve lenfosit sayılarında anlamlı farklılıklar gözlendi. Sistemik immün-inflamasyon indeksi değeri ektopik gebelik grubunda (890,70±545,30) intrauterin gebelik grubuna (1121,50±537,59, p=0,004) kıyasla anlamlı olarak daha yüksekti. Benzer şekilde, sistemik inflamatuvar yanıt indeksi ve pan-immün inflamatuvar değer ektopik gebelik grubunda anlamlı olarak yükselmiştir (sistemik inflamatuvar yanıt indeksi: 70,31±29,70 vs. 89,07±32,49, p=0,000; pan-immün inflamatuvar değer: 477,56±270,08 vs. 679,77±319,18, p=0,000). Alıcı işletim karakteristik eğrisi analizi, sırasıyla 0,670, 0,670 ve 0,710 eğri altında kalan alan değerleri ile bu belirteçler için orta düzeyde tanısal doğruluk göstermiştir.

Sonuç: Sistemik immün-inflamasyon indeksi, sistemik inflamatuar yanıt indeksi ve pan-immün inflamatuar değer gibi inflamatuar belirteçler ektopik gebelik için tanısal araçlar olarak potansiyel göstermektedir. Bu belirteçlerin klinik uygulamaya dahil edilmesi, geleneksel yöntemleri tamamlayarak tanısal doğruluğu artırabilir. Bu bulguları doğrulamak ve klinik uygulamalarını geliştirmek için daha büyük örneklem boyutlarıyla daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Ektopik gebelik, biyobelirteçler, enflamasyon, bağışıklık sistemi

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INTRODUCTION

Ectopic pregnancy (EP) is a pathological pregnancy condition that occurs when a fertilised ovum implants outside the uterus, typically in the fallopian tubes, but can also occur in the ovary, cervix or abdominal cavity (1). The incidence of EP is estimated to be between 1 and 2 percent of all pregnancies. In recent years, the frequency of diagnosis has increased due to improved early diagnosis methods and the development of more sensitive ultrasonography technologies (1). EP is considered an acute obstetric emergency with the potential to result in significant maternal morbidity and mortality if not diagnosed and treated in a timely manner and may result in significant complications such as tubal rupture, haemorrhagic shock and maternal death. Tubal rupture is clinically manifested by symptoms such as severe abdominal pain, vaginal bleeding and hypotension (1). Furthermore, failure to treat EP early may have adverse effects on future fertility and increase the risk of recurrent EP. Therefore, it is very important to diagnose EP early to prevent these complications (1).

Diagnostic methods currently used to diagnose EP include measurement of human coryonic gonadotropin (HCG) levels, transvaginal ultrasonography (TVUSG) and evaluation of serum progesterone levels. Transvaginal ultrasonography is one of the most effective methods to determine the localisation of EP. While HCG levels increase at a regular rate in normal intrauterine pregnancy, this increase is usually slow or irregular in EP. The combination of these two methods provides high sensitivity and specificity in the early diagnosis of EP (2-4).

The role of inflammatory response in EP has been an important area of interest for researchers in recent years. The inflammatory response is a defence mechanism initiated by the body in response to infection or tissue damage. In EP, abnormal localisation of the implanted embryo and associated tissue damage may play a role as a trigger for the inflammatory response (5,6).

The systemic inflammation index (SII) is a biomarker calculated using platelet (PLT), neutrophil (NEU) and lymphocyte (LYM) counts, and its formula is PLTxNEU/LYM. A high SII value is indicative of increased inflammatory activity in the body. In one study, it was shown that SII was elevated in patients with EP treated with surgery compared to patients treated with methotrexate (7). In another study, SII was identified as a valuable marker for predicting the risk of tubal EP rupture (8). A recent study showed that patients with low SII values responded better to methotrexate in the treatment of tubal EP (9).

Systemic immune response index (SIRI) is calculated using neutrophil (NEU), monocyte (MON) and lymphocyte (LYM) counts and is used to assess the severity of the inflammatory response. Although there is little literature examining the role of SIRI in EP, one study has shown that SIRI is elevated in caesarean scar pregnancies, potentially providing a diagnostic benefit in such cases (10).

Pan-immune inflammatory value (PIV) is used as a combined indicator of inflammatory processes and immune response. PIV is calculated using platelet (PLT), neutrophil (NEU), monocyte (MON) and lymphocyte (LYM) counts. At the time of our study, there were no publications in the literature on the relationship between PIV and EP.

Evaluation of the inflammatory response in EP is of great importance for early diagnosis and determination of appropriate treatment strategies. The use of inflammatory markers such as SII, SIRI and PIV may be valuable in clinical practice to determine the severity and treatment requirements of EP. The aim of our study was to examine the association of SII, SIRI and PIV values with EP and to determine whether they can be used as diagnostic tools.

MATERIALS AND METHODS

The study was initiated after the approval numbered AESH-EK1-2023-773 was obtained from the Ethics Committee of Ankara Etlik City Hospital and the study was conducted in accordance with the Declaration of Helsinki. The files of patients who were treated with the diagnosis of EP between November 2022 and September 2023 in our hospital and patients diagnosed with intrauterine pregnancy (IUP) presenting to the outpatient clinic were extracted. EP patients were classified as group-1 and IUP patients as group-2. Inclusion criteria for EP group;

1) Patients with tubal EP confirmed by ultrasonography,
2) Patients over 18 years of age
3) Patients with hemogram results at the time of diagnosis in the medical record

Our exclusion criteria for the EP group

1) Diagnosed with ruptured EP
2) Leukaemia, lymphoma and bone marrow diseases that may affect blood counts
3) Those with active infection
4) Patients with diseases that increase systemic inflammation (systemic lupus erythematosus, diabetes mellitus, hypertension, vasculitis, rheumatoid arthritis, renal failure, liver failure)
5) Heterotopic pregnancy and other ectopic pregnancies located outside the tuba uterina

Our inclusion criteria for the IUP group;

1) Pregnant women with intrauterine fetal cardiac activity detected by ultrasonography
2) Patients whose haemogram is checked at the first visit
3) Those over 18 years of age

Our exclusion criteria for the IUP group;

1) Those with leukaemia, lymphoma and bone marrow diseases that may affect blood counts
2) Those with active infection
3) Patients with diseases that increase systemic inflammation (systemic lupus erythematosus, diabetes mellitus, hypertension, vasculitis, rheumatoid arthritis, renal failure, liver failure)

As a result of the file search, 211 patients diagnosed with EP were found and when the inclusion and exclusion criteria were applied, it was seen that 153 patients could be included in the study. Among 153 EP patients, permutation randomisation was applied and 105 patients were included in group-1. In the cohort of 2455 patients diagnosed with IUP, 2104 patients were eligible for inclusion when inclusion and exclusion criteria were applied. A randomisation procedure based on permutations was applied to 2104 patients, resulting in the inclusion of 105 patients in Group 2.

After identifying patients who could be included in both groups, relevant data, i.e. age, gravida, parity, white blood cell (WBC), neutrophil (NEU), monocyte (MON), lymphocyte (LYM) and platelet (PLT) values were obtained from the medical records. These were used to calculate SII, SIRI and PIV values. The formula used to calculate SIRI is PLTxMON/LYM, formula is PLTxNEU/LYM for SII, the formula is expressed as PLTxMONxNEU/LEU for PIV.

In our hospital, blood samples of the patients are collected in a 3 mL BD Vacutainer™ Blood Collection K2EDTA tube (lot 4141891; Becton Dickinson, Plymouth, England) for complete blood count and measured by fluorescence flow cytometry method on a Sysmex XN-1000 (Sysmex Europe GmbH, Bornbarch 1, 22848 Norderstedt, Germany).

Statistical Analysis

In the power analysis performed pre-study, alpha-error: 0.05, beta-error: 0.95 and effect size: 0.5 (medium) were taken as alpha-error: 0.05, beta-error: 0.95 and effect size: 0.5 (medium) for analysis with t-test and it was decided to include a total of 210 patients with 105 patients in each group.

All data were entered into the statistical software SPSS version 25.0 (Armonk, NY, IBM Corp., USA) and analysed. Mann–Whitney U test was used to evaluate the gravida and parity values between IUP and EP groups. Independent t-test was used to evaluate age, neutrophil, monocyte, lymphocyte, platelet, SII, SIRI and PIV values between the groups. Logistic regression analysis was used for the diagnostic value, sensitivity and specificity analyses of SII, SIRI and PIV values for EP and area under the curve (AUC) values were determined by calculating the receiver operating characteristic (ROC) curve. Results were considered significant if the p-value was less than 0.05.

RESULTS

When the statistical analyses of the groups were performed, the mean age of group-1 and group-2 was 28.99±5.20 and 28.99±5.20 years, respectively, and there was no significant difference between them (p=0.745). Gravida and parity values were compared between the two groups using the Mann–Whitney U test, and no significant difference was observed (U=4387.0, p=0.949 and U=4364.0, p=0.895, respectively). The distribution of both variables was similar across the groups. The mean WBC values were 12.86±4.97 in group-1 and 10.91±1.96 in group-2 and there was a statistically significant difference between them (p=0.000). The mean PLT values of the groups were 231.24±59.71 and 251.32±53.50, respectively, and the difference between them was statistically significant (p=0.017). The mean NEU values were 6.58±1.68 in group-1 and 7.53±1.81 in group-2 and the difference between them was statistically significant (p=0.000). The mean value of MON was 0.55±0.15 in group-1 and 0.62±0.18 in group-2 and there was a significant difference between them (p=0.003). The mean LYM values of the groups were 2.34±0.65 and 1.80±0.43, respectively, and the difference between them was statistically significant (p=0.000). Mean SII values were 890.70±545.30 in group-1 and 1121.50±537.59 in group-2 and the difference between them was significant (p=0.004). Mean SIRI values were 70.31±29.70 in group-1 and 89.07±32.49 in group-2 and the difference between them was significant (p=0.000). The mean PIV values of the groups were 477.56±270.08 and 679.77±319.18, respectively, and there was a statistically significant difference between them (p=0.000) (Table 1).

ROC curve analysis for the use of SII value as a parameter in the diagnosis of ectopic pregnancy showed AUC 0.670, sensitivity 0.83 and specificity 0.50, which were found to be significant for this variable (p=0.007). Positive predictive value (PPV) was 0.57 and negative predictive value (NPV) was 0.79 (Table 2 and Figure 1). When ROC curve analysis was performed for the use of SIRI value as a parameter in the diagnosis of ectopic pregnancy, AUC 0.670, sensitivity 0.56 and specificity 0.72 were found to be significant

Table 1. Comparison of Variables According to Groups

Variable	Group-1 (EP) (n=105) Mean±Standard Deviation	Group-2 (IUP) (n=105) Mean±Standard Deviation	t- statistic	p- value
Age	28.99±5.20	28.73±5.41	0.325	0.745
White Blood Cell (*10^3/µl)	12.86±4.97	10.91±1.96	4.818	0.000*
Platelet (*10^3/µl)	231.24±59.71	251.32±53.50	-2.404	0.017*
Neutrophil (*10^3/µl)	6.58±1.68	7.53±1.81	-3.730	0.000*
Monocyte (*10^3/µl)	0.55±0.15	0.62±0.18	-2.989	0.003*
Lymphocyte (*10^3/µl)	2.34±0.65	1.80±0.43	6.550	0.000*
SII †	890.70±545.30	1121.50±537.59	-2.910	0.004*
SIRI ‡	70.31±29.70	89.07±32.49	-4.136	0.000*
PIV §	477.56±270.08	679.77±319.18	-4.716	0.000*
Variable	Group-1 (EP) (n=105) Median (IQR) **	Group-2 (IUP) (n=105) Median (IQR)	U value	p- value
Gravida	2 (1–2)	2 (1–2)	4387.0	0.949
Parita	1 (0–1)	1 (0–1)	4364.0	0.895

†: systemic immune-inflammation index. **‡:** systemic inflammatory response index**. §:** pan-immune inflammatory value *: statistically significant **: Interquartile Range

Table 2. Logistic Regression and ROC Results for SII Value

Parameter	Value	P Value	Threshold
ROC Area Under Curve	0.670	0.007*	764.80
Sensitivity	0.83		
Specificity	0.50		
Positive Predictive Value	0.57		
Negatif Predictive Value	0.79		

*: statistically significant

Table 3. Logistic Regression Results for SIRI Value

Parameter	Value	P Value	Threshold
ROC Area Under Curve	0.670	0.001*	82.67
Sensitivity	0.56		
Specificity	0.72		
Positive Predictive Value	0.62		
Negatif Predictive Value	0.67		

*: statistically significant

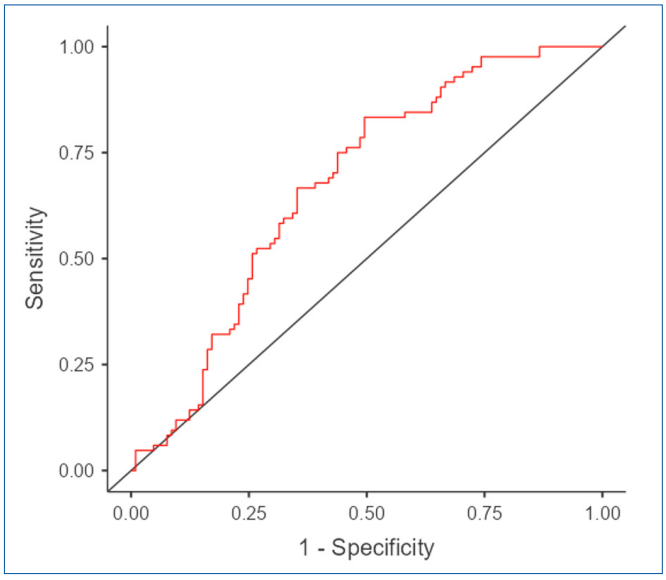

Figure 1. Receiver Operating Characteristic (ROC) Curve for SII

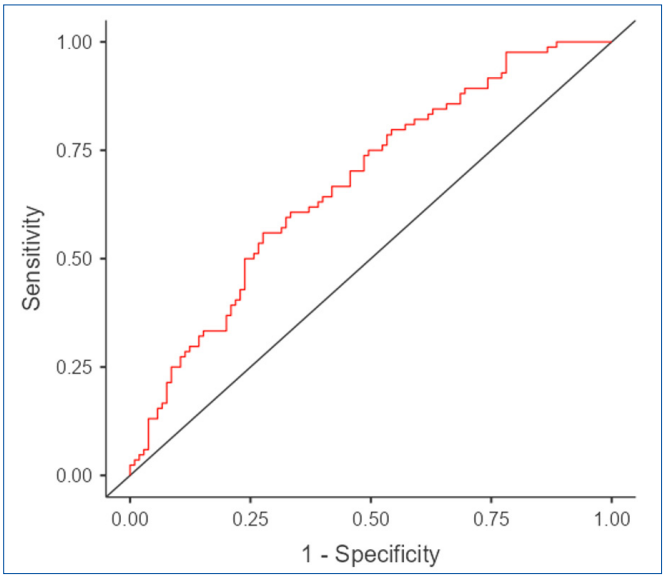

Figure 2. Receiver Operating Characteristic (ROC) Curve for SIRI

for this variable (p=0.001). PPV and NPV were 0.62 and 0.67, respectively (Table 3 and Figure 2). When ROC curve analysis was performed for the use of PIV value as a parameter in the diagnosis of ectopic pregnancy, AUC 0.710, sensitivity 0.56 and specificity 0.83 were found and found to be significant for this variable (p=0.000). PPV was 0.72 and NPV was 0.70 (Table 4 and Figure 3).

Table 4. Logistic Regression Results for PIV Value

Parametre	Value	P Value	Threshold
ROC Area Under Curve	0.710	0.000*	617.29
Sensitivity	0.56		
Specificity	0.83		
Positive Predictive Value	0.72		
Negatif Predictive Value	0.70		

*: statistically significant

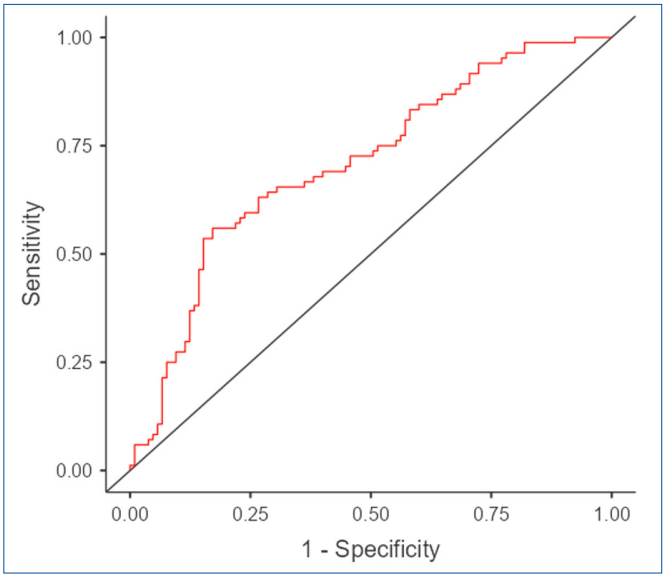

Figure 3. Receiver Operating Characteristic (ROC) Curve for PIV

DISCUSSION

Review of the literature shows that the studies examining the relationship between SII and EP are primarily concerned with the correlation between these factors and methotrexate response and the risk of rupture of EP (7-9). In contrast, SIRI has only been investigated in caesarean scar pregnancies and no study has examined the relationship between PIV and EP. The aim of this study was to analyse the diagnostic and prognostic value of inflammatory markers such as SII, SIRI and PIV in patients diagnosed with EP. The findings suggest that these inflammatory markers may be effective in the diagnosis and treatment of EP. In addition, a noteworthy aspect of this study is that it is one of the first to analyse the relationship between EP and SIRI and PIV.

Embryo implantation is a complex and critical process in which the embryo attaches to the endometrium and initiates pregnancy. Successful implantation of the embryo into the endometrium requires the coordination of multiple biochemical and cellular events. A considerable amount of evidence suggests that inflammation is a crucial factor in this process and has the potential to influence the success of implantation (11). The role of inflammation in processes such as decidualisation of stromal cells and enhancement of endometrial receptivity during embryo implantation is critical. These processes are associated with high levels of pro-inflammatory cytokines and prostaglandins (11). An inflammatory environment is necessary for the attachment and invasion stages of the blastocyst. This is achieved by appropriate guidance of the innate immune system by the trophoblast (12). The role of inflammation in the process of embryo implantation is critical for successful implantation of the embryo into the endometrium. Molecules such as pro-inflammatory cytokines, prostaglandins and immunomodulators play a very important role in this process and ensure the success of implantation by increasing endometrial receptivity (11-13). In our study, SII, SIRI and PIV values were higher in the group with live pregnancy compared to the EP group. We consider that inflammation should increase during embryo implantation in IUP and the observed low inflammatory values may be attributed to abnormal implantation formation in EP.

In the literature, there are studies showing that inflammatory markers other than SII, SIRI and PIV are increased in EP. In the study by Ülkümen et al., lower platelet count was observed in the EP group compared to the IUP group, and this finding was similar in our study (6). Mean platelet volume value (MPV), which is an inflammatory marker, was found to be significantly higher in Karaman et al. study, whereas no significant difference was observed in the other study (5). Although MPV is an inflammatory marker, it is less effective than SII, SIRI and PIV in showing inflammation. Although the literature examining the role of SIRI in EP is scarce, one study has shown that SIRI is elevated in caesarean scar pregnancies and potentially provides diagnostic utility (10). However, the low SIRI values observed in tubal EPs in our study suggest that this may be specific to caesarean scar pregnancies.

The results of the ROC analysis showed that SII is an important diagnostic indicator for EP with an AUC of 0.670, sensitivity of 83% and specificity of 50%. In the light of these findings, it can be said that SII has a moderate accuracy rate in the diagnosis of EP and can serve as a valid marker in clinical practice. In the ROC analysis, SIRI was found to have an AUC of 0.670, a sensitivity of 56% and a specificity of 72% in the diagnosis of EP. In the light of these findings, it seems reasonable to suggest that SIRI can be used as a diagnostic tool for EP with a moderate accuracy rate. The results of the ROC analysis of the PIV revealed an AUC of 0.710, a sensitivity of 56% and a specificity of 83% for the diagnosis of EP. We believe that PIV has a middle degree of accuracy in the diagnosis of EP and can be used as a marker in clinical practice.

Currently, serum HCG and progesterone levels have an important value as biochemical parameters in the diagnosis of EP. It has been reported that the sensitivity of HCG in the diagnosis of EP ranges

between 96% and 100% and the specificity between 79% and 100% (2,14). Similarly, it was reported that the sensitivity of serum progesterone value in the diagnosis of EP ranged between 63% and 100%, and the specificity ranged between 35% and 100% (3,15,16). The findings of our study suggest that SII, SIRI and PIV values can be used as complementary parameters in the diagnosis of EP together with serum progesterone levels, especially in cases where β-HCG elevation is minimal.

CONCLUSION

This study shows that inflammatory markers such as SII, SIRI and PIV may play an important role in the diagnosis and management of EP. These markers may be valuable in clinical practice to determine the severity and treatment requirements of EP. Further studies are needed to confirm these findings and to finalise the status of the use of inflammatory markers in clinical practice. Furthermore, additional studies in different patient groups and with larger sample sizes will further clarify the diagnostic and prognostic value of these markers.

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HPV Pozitifliğinin Gebelik Planlamasına Etkisi: Bilgi, Psikososyal Tepkiler ve Davranışsal Sonuçların Kesitsel Analizi

The Impact of HPV Positivity on Pregnancy Planning: A Cross-Sectional Analysis of Knowledge, Psychosocial Responses, and Behavioral Outcomes

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ÖZ

Amaç: İnsan Papillomavirus (HPV) enfeksiyonu, kadın sağlığı açısından önemli bir halk sağlığı sorunu olup, üreme çağındaki kadınlarda gebelik planlamasını etkileyebilmektedir. Bu çalışma, HPV pozitif kadınların bilgi düzeylerini, psikososyal tepkilerini ve gebelik planlamasına ilişkin davranışlarını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu kesitsel çalışma, HPV pozitifliği nedeniyle jinekolojik onkoloji polikliniğine başvuran, 18–44 yaş arası kadınlar üzerinde gerçekleştirilmiştir. Katılımcılar, sosyodemografik özellikler, HPV'ye ilişkin bilgi düzeyleri ve psikososyal etkilerini değerlendiren 21 soruluk yapılandırılmış bir anket doldurmuştur. Veriler SPSS Version 29 programı kullanılarak analiz edilmiştir.

Bulgular: Çalışmaya toplam 152 HPV pozitif kadın dahil edilmiştir. Katılımcıların ortalama yaşı 34,2±5,6 yıl olup, %61,2'si evlidir. HPV tanısı sonrası katılımcıların %28,3'ü gebelik planında değişiklik yaptığını, %14,5'i etkilenmediğini, %57,2'si ise halihazırda gebelik planı bulunmadığını bildirmiştir. Gebelik planını değiştirenlerde en sık nedenler; vertikal bulaş korkusu (%46,5), partnerle ilişkili sorunlar (%25,6) ve kendini sağlıksız hissetme (%23,3) olarak belirlenmiştir. Yaş grubu (p=0.022), medeni durum (p=0.037) ve eğitim düzeyi (p=0.024) gebelik planı değişikliğiyle anlamlı ilişki göstermiştir. HPV'nin gebeliği etkilediğine (p=0.003) ve bebeğe bulaşabileceğine (p=0.008) inanma, gebelik planında değişiklik için anlamlı belirleyicilerdir. Kaygı, benlik algısı ve psikolojik destek ihtiyacı gibi psikososyal değişkenlerle anlamlı ilişki saptanmamıştır (p>0.05). Bulgular, HPV tanısı sonrası özellikle üreme çağında, evli ve ortaöğretim düzeyindeki kadınların yanlış inanışlar ve enfeksiyona bağlı kaygılar nedeniyle gebelik planlarını daha sık değiştirdiğini göstermektedir.

Sonuç: Sonuçlar, HPV pozitifliğinin özellikle belirli sosyodemografik gruplarda gebelik planlama kararlarını etkileyebildiğini göstermektedir. Yanlış inanışlar ve bilgi eksikliği, gereksiz gebelik ertelemelerine neden olabileceğinden, hedefe yönelik eğitim ve psikososyal destek programlarının geliştirilmesi kritik önem taşımaktadır.

Anahtar Kelimeler: İnsan papillomavirüsü, gebelik planlaması, fertilite kaygıları, üreme sağlığı, psikososyal etki, vertikal bulaş

ABSTRACT

Aim: Human Papillomavirus (HPV) infection is a major public health concern in women's health and may influence pregnancy planning in women of reproductive age. This study aims to evaluate the knowledge levels, psychosocial responses, and behaviors related to pregnancy planning among HPV-positive women.

Materials and Methods: This cross-sectional study was conducted among women aged 18–44 who visited the gynecological oncology outpatient clinic due to HPV positivity. Participants completed a 21-item structured questionnaire assessing sociodemographic characteristics, HPV-related knowledge, and psychosocial effects. Data were analyzed using the SPSS version 29.

Results: A total of 152 HPV-positive women were included in the study. The mean age of the participants was 34.2±5.6 years, and 61.2% were married. After the HPV diagnosis, 28.3% of the participants reported a change in their pregnancy plans, 14.5% reported no change, and 57.2% reported that they did not have pregnancy plans. The most common reasons for changing pregnancy plans were fear of vertical transmission (46.5%), partner-related concerns (25.6%), and perceived poor health (23.3%). Age group (p=0.022), marital status (p=0.037), and education level (p=0.024) showed a significant association with pregnancy plan changes. Belief that HPV affects pregnancy (p=0.003) and can be transmitted to the baby (p=0.008) were significant predictors of pregnancy plan changes. No significant relationship was found with psychosocial variables such as anxiety, self-perception, and need for psychological support (p>0.05). The findings suggest that women of reproductive age, married women, and those with a secondary education level are more likely to alter their pregnancy plans after an HPV diagnosis, mainly due to misconceptions and infection-related anxiety.

Discussion: The findings indicate that HPV positivity may influence pregnancy planning decisions, particularly among certain sociodemographic groups. Since misconceptions and lack of information may lead to unnecessary pregnancy delays, targeted education and psychosocial support programs are of critical importance.

Keywords: Human papillomavirus, pregnancy intention, fertility concerns, reproductive health, psychosocial impact, health behavior, vertical transmission

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GİRİŞ

İnsan Papillomavirus (HPV), dünya genelinde en yaygın cinsel yolla bulaşan enfeksiyonlardan biri olup yalnızca servikal kanserin değil, anogenital ve orofaringeal malignitelerin de başlıca etkeni olarak tanımlanmaktadır (1). HPV'nin klinik önemi, malignite riskiyle sınırlı değildir; infertilite açısından potansiyel bir risk faktörü olması, gebelikte preterm doğum ve düşük doğum ağırlığı gibi obstetrik komplikasyonlarla ilişkilendirilmesi ve anne–çocuk arasında vertikal bulaş olasılığı, kadın sağlığı üzerinde çok boyutlu etkiler oluşturmaktadır (2,3).

Her ne kadar HPV enfeksiyonlarının büyük bir kısmı geçici ve asemptomatik seyretse de, pozitif tanı alan kadınlarda anksiyete, depresyon, damgalanma ve cinsel işlev kaybı gibi psikososyal sonuçlar literatürde sıkça rapor edilmektedir (4-6). Bu biyolojik ve psikososyal yükün yanı sıra, kültürel inançlar, bilgi eksikliği, sosyal stigma ve çelişkili tıbbi öneriler, kadınların gebelik planlamasına ilişkin karar verme süreçlerini daha da karmaşıklaştırmaktadır. Özellikle gebelikte yüksek HPV viral yükünün vertikal geçiş ve preterm doğum riskini artırabileceğine dair bulgular (7,8), kadınların üreme sağlığına ilişkin algılarını ve sağlık profesyonellerine duydukları güveni doğrudan etkilemektedir.

Türkiye bağlamında değerlendirildiğinde, HPV ve HPV aşısına yönelik farkındalık düzeyinin görece düşük olması, bu süreci daha da zorlaştırmaktadır. Yapılan epidemiyolojik çalışmalar, genç kadınların yalnızca %41,6'sının HPV hakkında bilgi sahibi olduğunu ve sadece %27,9'unun aşının servikal kanseri önleyici etkisini doğru biçimde ifade edebildiğini göstermektedir (9). Bu bulgular, HPV tanısının kadınlar açısından yalnızca klinik bir olgu değil, aynı zamanda psikolojik, sosyokültürel ve toplumsal boyutlarıyla da değerlendirilmesi gerektiğini gösterir.

Bu çalışmada, HPV pozitifliği tanısı olan üreme çağındaki kadınların gebelik planlamasına ilişkin bilgi, tutum ve davranışlarının kapsamlı biçimde değerlendirilmesi amaçlanmaktadır. Ayrıca HPV pozitifliğinin doğurganlık kararları, psikolojik iyilik hâli, algılanan hastalık yükü ve tıbbi danışmanlığa duyulan güven üzerindeki etkilerini incelenecektir. Çalışmanın temel hipotezi, HPV pozitifliğinin gebelik planlaması ve üreme sağlığına ilişkin tutumları anlamlı ölçüde etkilediğidir.

GEREÇ VE YÖNTEMLER

Bu kesitsel ve anket tabanlı çalışma, ikinci basamak bir hastanenin Jinekolojik Onkoloji Cerrahisi polikliniğinde yürütülmüştür. Çalışma protokolü, Kırıkkale Üniversitesi Etik Kurulu tarafından onaylanmıştır (Onay Tarihi: 28 Mayıs 2025; Karar No: 2025.05.43). Tüm katılımcılardan yazılı bilgilendirilmiş onam alınmış, yanıtlar anonim olarak kaydedilmiştir. Katılım gönüllülük esasına dayanmış olup çalışma, Helsinki Bildirgesi ilkelerine uygun biçimde gerçekleştirilmiştir.

Çalışma popülasyonu, daha önce yüksek riskli HPV enfeksiyonu tanısı almış, 18-44 yaş aralığında toplam 152 kadından oluşmaktadır. Katılımcılar, jinekoloji polikliniğine rutin takip amacıyla başvuran hastalar arasından ardışık örnekleme yöntemiyle seçilmiştir. Dahil edilme kriterleri; üreme çağında olmak, laboratuvar testleriyle doğrulanmış yüksek riskli HPV pozitifliğine sahip olmak ve daha önce rahim ağzı kanseri ya da preinvaziv servikal lezyon tanısı almamış olmaktır. Bilinen infertilitesi olan ya da menopozal dönemde olanlar, servikal neoplazi nedeniyle aktif tedavi görenler ile anketi doldurma kapasitesini etkileyebilecek kognitif veya psikiyatrik rahatsızlığı bulunanlar çalışma dışında bırakılmıştır.

Veriler, ilgili literatürün kapsamlı incelemesi ve daha önce valide edilmiş ölçeklerden yararlanılarak geliştirilen 21 sorudan oluşan yapılandırılmış ve kendi kendine doldurulan bir anket aracılığıyla toplanmıştır. Anket; katılımcıların sosyodemografik özelliklerini, üreme öyküsü ve gebelik planlarını, HPV'ye ilişkin bilgi düzeylerini, HPV tanısının psikolojik ve davranışsal etkilerini, gebelik ve fetüse yönelik risk algılarını, sağlık hizmeti sağlayıcılarıyla iletişim ve danışmanlık deneyimleri ile HPV aşısına yönelik tutumlarını değerlendirmiştir. Katılımcıların HPV tanısı sonrası kaygı düzeyi, beşli Likert ölçeği (1: çok düşük, 5: çok yüksek) kullanılarak ölçülmüştür (10). Anketin tamamlanma süresi ortalama 10–15 dakika olarak belirlenmiştir.

İstatistiksel Analiz

İstatistiksel analizler, IBM SPSS Statistics 29 yazılımı kullanılarak gerçekleştirilmiştir. Kategorik değişkenler frekans ve yüzde (%) değerleri ile sunulmuş, değişkenler arasındaki ilişkiler Ki-kare testi ile değerlendirilmiştir. Tüm analizlerde $p < 0,05$ değeri istatistiksel olarak anlamlı kabul edilmiştir. Analizlerin planlanmasında, orta düzey etki büyüklüğü (Cohen's $w = 0,30$) ve %80 test gücü ($1-\beta = 0,80$) dikkate alınarak minimum örneklem büyüklüğü yaklaşık 143 olarak hesaplanmıştır. Çalışmada 152 katılımcının yer alması, analizlerin yeterli istatistiksel güçle yürütülmesini sağlamaktadır.

BULGULAR

Katılımcıların Demografik Özellikleri

Çalışmaya toplam 152 kadın katılmıştır. Katılımcıların yaş dağılımı incelendiğinde, %6,6'sı 18–24 yaş, %36,8'i 25–34 yaş ve %56,6'sı 35–44 yaş grubunda yer almaktaydı. Katılımcıların

Tablo 1. Katılımcıların Sosyodemografik Özellikleri

Sorular	Cevaplar	Sayı (n)	%
Yaş grubu	18-24	10	6,6
	25-34	56	36,8
	35-44	86	56,6
Medeni durum	bekar	23	15,1
	evli	93	61,2
	boşanmış	36	23,7
Eğitim düzeyi	ilkokul	32	21,1
	ortaokul	27	17,8
	lise	44	28,9
	üniversite	49	32,2
Çocuk sahibi	evet	113	74,3
	hayır	39	25,7
Gebelik planı	evet	48	31,6
	hayır	104	68,4

medeni durumlarına bakıldığında %15,1'i bekar, %61,2'si evli ve %23,7'si boşanmıştı. Eğitim düzeyi açısından değerlendirildiğinde, %21,1'i ilkokul, %17,8'i ortaokul, %28,9'u lise ve %32,2'si üniversite mezunuydu. Katılımcıların %74,3'ünün çocuk sahibi olduğu, %25,7'sinin ise çocuk sahibi olmadığı görüldü. Gelecekte gebelik planına ilişkin yanıtlarda, %31,6'sı gebelik planladığını, %68,4'ü planlamadığını belirtmiştir. Katılımcıların sosyodemografik ve doğurganlık özelliklerine ilişkin bulguların dağılımı Tablo 1'de verilmiştir

HPV ile İlgili Bilgi Düzeyi ve Algılar

Katılımcıların HPV hakkındaki bilgi düzeyleri ve algıları Tablo 2'de özetlenmiştir. Katılımcıların %77,6'sı HPV'nin genellikle cinsel yolla bulaşan bir virüs olduğunu bildiğini ifade etmiştir. HPV'nin gebeliği doğrudan etkilediğini düşünenlerin oranı %31,6 iken, %39,5'i bu konuda kararsız olduğunu belirtmiştir. Katılımcıların %36,8'i HPV'nin bebeğe bulaşabileceğini düşündüğünü, %52,6'sı ise emin olmadığını ifade etmiştir. HPV'nin çoğu zaman kendiliğinden geçebildiğini bilenlerin oranı %42,1, bilmeyenlerin oranı %41,4, kararsızların oranı ise %16,4'tir. HPV'nin her zaman kanserle sonuçlanmadığını bilenler %63,8, bilmeyenler %19,1, emin olmayanlar ise %17,1'dir. Katılımcıların büyük çoğunluğu (%82,9), HPV'nin rahim ağzı kanseriyle ilişkili olduğunu bilmektedir. Bununla birlikte, rahim ağzı kanseri aşısı yaptıranların oranı yalnızca %9,2 olup, %90,2'sinin aşı yaptırmadığı görülmüştür.

Katılımcıların HPV Tanısı Sonrası Üreme Sağlığı ve Cinsel Yaşam Tutumları

Katılımcıların HPV tanısı sonrası yaşadıkları psikososyal etki, cinsel yaşam tutumları ve gebelik planı etkilerine ilişkin bulgular Tablo 3'te özetlenmiştir.

Katılımcıların büyük çoğunluğu (%63,2) HPV pozitifliği tanısını son 6 ay içinde almıştır. Daha önce tanı aldığını belirtenlerin %9,9'u 6–12 ay önce, %15,8'i 1–2 yıl önce ve %11,2'si 2 yıldan uzun süre önce tanı konulduğunu ifade etmiştir. Katılımcıların kaygı düzeyi ortalaması 3,55±1,37 olup orta-yüksek düzeyde olduğu belirlenmiştir. %52,6'si yüksek kaygı düzeyini (4-5), %27,6'sı ise orta düzey (3) kaygı ve %19,8'i de düşük kaygı (1–2) düzeyinde olduğunu ifade etmişlerdir. Katılımcıların %35,5'i kendini 'hasta' gibi hissettiğini, %40,1'i HPV tanısının özgüvenini olumsuz etkilediğini ifade etmiştir. Tanı sonrası psikolojik destek alma ihtiyacı %21,7 oranında belirtilmiş, ancak %9,9'u destek ihtiyacı hissetmesine rağmen bu hizmete ulaşamadığını bildirmiştir. Takip planının katılımcılara aktarımı konusunda ise %30,3'ü bilgilerin açık ve anlaşılır şekilde verildiğini, %33,6'sı bu bilgilendirmenin yetersiz olduğunu, %28,3'ü ise kısmen yeterli olduğunu ifade etmiştir.

HPV tanısının cinsel yaşamı olumsuz etkilediğini belirtenlerin oranı %38,2 iken, %33,6'sı herhangi bir etkilenme yaşamadığını, %28,3'ü ise emin olmadığını ifade etmiştir. Gebelik planlarında değişiklik olduğunu belirtenlerin %15,8'i gebeliği ertelediğini, %12,5'i ise tamamen vazgeçtiğini bildirmiştir. Katılımcıların %14,5'i tanının gebelik planını etkilemediğini, %57,2'si ise zaten gebelik düşünmediğini ifade etmiştir. Buna göre HPV tanısı aldıktan sonra gebelik planlamasında değişiklik yapanların oranı %28,3, yapmayanların oranı %14,5 ve gebelik planı olmayanların oranı ise %57,2'dir. Kişilerin gebelik planını etkileyen başlıca faktörler arasında bebeğe bulaşma korkusu (%46,5), partnerle yaşanan sorunlar (%25,6), kendini hasta gibi hissetme (%23,3) ve toplumsal baskı/sosyal çevre (%4,7) olarak saptanmıştır.

İlişki Analizleri

Katılımcıların gebelik planındaki değişikliği ile sosyodemografik faktörler, HPV ile ilgili bilgi düzeyi ve algıları, HPV tanısı ve tanı

Tablo 2. Katılımcıların HPV ile İlgili Bilgi Düzeyi ve Algıları

Sorular	Evet		Hayır		Emin değilim	
	n	%	n	%	n	%
HPV'nin genellikle cinsel yolla bulaşan bir virüs olduğunu biliyor musunuz	118	77,6	34	22,4	-	-
HPV'nin gebeliği doğrudan etkilediğini düşünüyor musunuz?	48	31,6	44	28,9	60	39,5
HPV'nin bebeğe bulaşabileceğini düşünüyor musunuz?	56	36,8	16	10,5	80	52,6
HPV'nin çoğu zaman kendiliğinden geçtiğini biliyor musunuz	64	42,1	63	41,4	25	16,4
HPV'nin her zaman kanserle sonuçlanmadığını biliyor musunuz?	97	63,8	29	19,1	26	17,1
HPV'nin rahim ağzı kanseriyle ilişkili olduğunu biliyor musunuz?	126	82,9	26	17,1	-	-
Rahim ağzı kanseri aşısı yaptırdınız mı ?	14	9,2	138	90,8	-	-

Tablo 3. Katılımcıların HPV Tanısı Sonrası Psikososyal Durumları ve Üreme Davranışlarına İlişkin Bulgular

Sorular	Cevaplar	n	%
HPV pozitif tanısını ne zaman aldınız?	Son 6 ay içinde 6–12 ay önce 1–2 yıl önce 2 yıldan uzun süre önce	96 15 24 17	63,2 9,9 15,8 11,2
Kaygı düzeyiniz (1: çok düşük – 5: çok yüksek):	1 2 3 4 5	20 10 42 27 53	13,2 6,6 27,6 17,8 34,9
Kendinizi "hasta" gibi hissediyor musunuz?	Evet Hayır	54 98	35,5 64,5
HPV tanınızın özgüveninizi etkiledi mi?	Evet Hayır	61 91	40,1 59,9
Tanı sonrası psikolojik destek alma ihtiyacı hissettiniz mi?	Evet Hayır Hissettim ama ulaşamadım	33 104 15	21,7 68,4 9,9
HPV tanısından sonra takip planınız size açık ve anlaşılır şekilde anlatıldı mı?	Evet Hayır Kısmen	46 50 56	30,3 32,9 36,8
HPV tanınızın cinsel yaşamınızı olumsuz etkilediğini düşünüyor musunuz?	Evet Hayır Emin değilim	58 51 43	38,2 33,6 28,3
HPV tanısı aldıktan sonra gebelik planlamanızda bir değişiklik oldu mu?	Gebelik planımı erteledim (Evet) Gebelikten tamamen vazgeçtim (Evet) Etkilenmedi (Hayır) Zaten gebelik planlamıyordum	24 19 22 87	15,8 12,5 14,5 57,2
HPV tanısı nedeniyle gebelik planınızı etkileyen faktör nedir?*	Bebeğe bulaşma korkusu Partnerimle yaşadığım sorunlar Kendimi hasta gibi hissetmem Toplumsal baskı/sosyal çevre	20 11 10 2	46,5 25,6 23,3 4,7

*Gebelik planı etkilenen 43 katılımcı için

sonrası psikososyal özellikleri arasındaki olası ilişkiler, Ki-kare testi kullanılarak incelenmiştir.

Tablo 4'te HPV tanısı sonrası gebelik planındaki değişim ile sosyodemografik faktörler arasındaki ilişki incelenmiştir. Bulgulara göre, yaş grupları arasında anlamlı farklılık saptanmıştır (p=0,022). Özellikle 25–34 yaş grubundaki kadınlarda HPV tanısının gebelik planını etkileme oranı (%41,1), diğer yaş gruplarına kıyasla daha yüksektir. Buna karşın 35–44 yaş grubunda katılımcıların büyük bölümü gebelik planlamadığını belirtmiştir. Medeni durum açısından bakıldığında da anlamlı bir ilişki bulunmuştur (p=0,037). Evli kadınların %35,5'i HPV tanısı sonrası gebelik planında

Tablo 4. HPV Tanısı Sonrası Gebelik Planındaki Değişim ile Sosyodemografik Faktörler Arasındaki İlişkinin Değerlendirilmesi

Sorular	Cevaplar	HPV Tanısı Sonrası Gebelik Planı Değişikliği			Ki-Kare Testi Olasılık
		Evet n (%)	Hayır n (%)	Gebelik Planı Olmayanlarn (%)	
Yaş grubu	18-24 25-34 35-44	3(%30,0) 23(%41,1) 17(%19,8)	0(%0,0) 10(%17,9) 12(%14,0)	7 (%70,0) 23 (%41,1) 57 (%66,3)	χ^2= 11,428 **p= 0,022**
Medeni durum	Bekar Evli Boşanmış	4(%17,4) 33(%35,5) 6(%16,7)	6(%26,1) 13(%14,0) 3(%8,3)	13(%56,5) 47(%50,5) 27(%75,0)	χ^2= 10,199 **p= 0,037**
Eğitim düzeyi	Ilkokul Ortaokul Lise Üniversite	2(%6,3) 13(%48,1) 15(%34,1) 13(%26,5)	6(%18,8) 2(%7,4) 5(%11,4) 9(%18,4)	24(%75,0) 12(%44,4) 24(%54,5) 27(%55,1)	χ^2=14,609 **p= 0,024**
Çocuk sahibi olma durumu	Evet Hayır	33(%29,2) 10(%25,6)	14(%12,4) 8(%20,5)	66(%58,4) 21(%53,8)	χ^2= 1,557 p= 0.459
Gebelik planı	Evet Hayır	43(%87,8) 0(%0,0)	5(%10,4) 17(%16,3)	0(%0,0) 87(%83,7)	χ^2=134,118 **p <0,001**

Not: İstatistiksel anlamlılık düzeyi p<0,05 olarak alınmıştır.

Tablo 5. HPV Tanısı Sonrası Gebelik Planında Değişiklik ile HPV'ye İlişkin Bilgi ve Algılar Arasındaki İlişkinin Değerlendirilmesi

Sorular	Cevaplar	HPV Tanısı Sonrası Gebelik Planı Değişikliği			Ki-Kare Testi Olasılık
		Evet n (%)	Hayır n (%)	Gebelik Planı Olmayanlar n (%)	
HPV'nin genellikle cinsel yolla bulaşan bir virüs olduğunu biliyor musunuz?	Evet Hayır	31(%26,3) 12(%35,3)	19(%16,1) 3(%8,8)	68(%57,6) 19(%55,9)	χ^2= 1,740 p= 0,419
HPV'nin gebeliği doğrudan etkilediğini düşünüyor musunuz?	Evet Hayır Emin değilim	15(%31,3) 12(%27,3) 16(%26,7)	3(%6,3) 14(%31,8) 5(%8,3)	30(%62,5) 18(%40,9) 39(%65,0)	χ^2= 16,085 **p= 0,003**
HPV'nin bebeğe bulaşabileceğini düşünüyor musunuz?	Evet Hayır Emin değilim	21(%37,5) 2(%12,5) 20(%25,0)	11(%19,6) 5(%31,3) 6(%7,5)	24(%42,9) 9(%56,3) 54(%67,5)	χ^2= 13,726 **p= 0,008**
HPV'nin çoğu zaman kendiliğinden geçtiğini biliyor musunuz?	Evet Hayır Emin değilim	20(%31,3) 19(%30,2) 4(%16,0)	12(%18,8) 8(%12,7) 2(%8,0)	32(%50,0) 36(%57,1) 19(%76,0)	χ^2= 5,404 p= 0,248
HPV'nin her zaman kanserle sonuçlanmadığını biliyor musunuz?	Evet Hayır Emin değilim	26(%26,8) 12(%41,4) 5(%19,2)	16(%16,5) 4(%13,8) 2(%7,7)	55(%56,7) 13(%44,8) 19(%73,1)	χ^2= 5,620 p= 0,229
HPV'nin rahim ağzı kanseriyle ilişkili olduğunu biliyor musunuz?	Evet Hayır	33(%26,2) 10(%38,5)	18(%14,3) 4(%15,4)	75(%59,5) 12(%46,2)	χ^2= 1,838 p= 0,399
Rahim ağzı kanseri aşısı yaptırdınız mı?	Evet Hayır	2(%14,3) 41(%29,7)	3(%21,4) 19(%13,8)	9(%64,3) 78(%56,5)	χ^2= 1,718 p = 0,424

Not: İstatistiksel anlamlılık düzeyi p<0,05 olarak alınmıştır.

değişiklik yaptığını ifade ederken, bekar ve boşanmış kadınlarda bu oran belirgin olarak düşüktür. Eğitim düzeyine göre dağılım incelendiğinde, fark istatistiksel olarak anlamlıdır (p=0.024); en yüksek değişim oranı ortaokul mezunlarında (%48,1) görülmüştür. Gebelik planlayan kadınlarda ise HPV tanısının gebelik planlarını etkileme oranı oldukça yüksektir (%87,8) ve bu fark istatistiksel olarak yüksek düzeyde anlamlı bulunmuştur (p<0,001). Buna karşın çocuk sahibi olma durumu gebelik planındaki değişiklikle anlamlı ilişki göstermemiştir (p=0.459).

Tablo 5'te HPV'ye ilişkin bilgi düzeyi ve algılar ile HPV tanısı sonrası gebelik planındaki değişim arasındaki ilişki incelenmiştir. HPV'nin gebeliği doğrudan etkilediğini düşünen kadınlarda, gebelik planını değiştirme oranı %31,3 iken, bu görüşe katılmayanlarda oran %27,3, emin olmayanlarda ise %26,7 olarak belirlenmiş olup bu durum istatistiksel olarak anlamlı bulunmuştur (p=0.003). Bu bulgu, HPV'nin gebelik sürecini olumsuz etkileyebileceği düşüncesinin, kadınların gebelik kararlarını yeniden değerlendirmelerine yol açtığını göstermektedir. Benzer

Tablo 6. HPV Tanısı Sonrası Gebelik Planında Değişim ile Tanı Süreci ve Psikososyal Faktörler Arasındaki İlişkinin Değerlendirilmesi

Sorular	Cevaplar	HPV Tanısı Sonrası Gebelik Planı Değişikliği			Ki-Kare Testi Olasılık
		Evet n (%)	Hayır n (%)	Gebelik Planı Olmayanlar n (%)	
HPV pozitif tanısını ne zaman aldınız?	Son 6 ay içinde 6 aydan önce	32(%33,3) 11(%19,6)	15(%15,6) 7(%12,5)	49(%51,0) 38(%67,9)	χ^2= 4,329 p= 0.115
Kaygı düzeyiniz: (1: çok düşük – 5: çok yüksek):	1-2 3 4-5	5(%16,7) 13(%31,0) 25(%31,3)	4(%13,3) 8(%19,0) 10(%12,5)	21(%70,0) 21(%50,0) 45(%56,3)	χ^2= 3,887 p=0.422
Kendinizi "hasta" gibi hissediyor musunuz?	Evet Hayır	19(%35,2) 24(%24,5)	8(%14,8) 14(%14,3)	27(%50,0) 60(%61,2)	χ^2= 2,181 p=0.336
HPV tanınız özgüveninizi etkiledi mi?	Evet Hayır	20(%32,8) 23(%25,3)	8(%13,1) 14(%15,4)	33(%54,1) 54(%59,3)	χ^2= 1,034 p=0.596
Tanı sonrası psikolojik destek alma ihtiyacı hissettiniz mi?	Evet Hayır	13(%27,1) 30(%28,8)	5(%10,4) 17(%16,3)	30(%62,5) 57(%54,8)	χ^2= 1,173 p=0.556
HPV tanısından sonra takip planınız size açık ve anlaşılır şekilde anlatıldı mı?	Evet Hayır	29(%28,4) 14(%28,0)	13(%12,7) 9(%18,0)	60(%58,8) 27(%54,0)	χ^2= 0,779 p=0.677

Soru alt grupları, analiz varsayımları için uygun şekilde birleştirme yapılmıştır.

şekilde, HPV'nin bebeğe bulaşabileceğini düşünen kadınlarda gebelik planını değiştirme oranı %37,5 olup, bu oran "bebeğe bulaşmayacağını" düşünenlerde %12,5'e düşmektedir ve istatistiksel olarak anlamlı bulunmuştur (p=0,008). Bu durum, olası bulaşma korkusunun kadınların gebelik planlamasında önemli bir belirleyici olduğunu ortaya koymaktadır. Buna karşın, katılımcıların HPV'nin bulaşma yolu, kansere dönüşme olasılığı veya rahim ağzı kanseri aşısına ilişkin bilgi düzeyleri ile gebelik planındaki değişiklik arasında anlamlı bir ilişki bulunmamıştır (p>0,05). Genel olarak, HPV'ye ilişkin gebelik ve bebek sağlığına yönelik endişeler, kadınların gebelik planlarını etkileyen en önemli faktörler olarak öne çıkmıştır.

Tablo 6'da, katılımcıların HPV pozitif tanı süresi ile tanı sonrası psikososyal etkilerinin, gebelik planlarındaki değişim üzerindeki olası etkileri analiz edilmiştir. Son 6 ay içinde veya daha önce tanı alan katılımcılar arasında gebelik planında değişiklik yapma eğilimi gözlemlense de, bu farkların istatistiksel olarak anlamlı çıkmamıştır. Benzer şekilde, kaygı düzeyi, kendini "hasta" hissetme durumu, HPV tanısının özgüvene etkisi, tanı sonrası psikolojik destek ihtiyacı ve takip planının açıklığı değişkenleri de gebelik planındaki değişim ile anlamlı bir ilişki göstermemiştir (p>0,05).

TARTIŞMA

Bu kesitsel çalışmanın bulguları, HPV pozitifliği olan kadınlarda gebelik planlaması kararlarının belirli demografik gruplarda daha fazla etkilendiğini göstermektedir. Özellikle 25–34 yaş aralığında olup evli ve eğitim düzeyi ortaöğretim olan kadınlarda, HPV tanısı sonrasında gebelik planlarını erteleme ya da yeniden değerlendirme eğilimi anlamlı derecede yüksektir. Bu durum, üreme çağının ortalarında yer alan kadınların, HPV'nin üreme sağlığına olası etkilerine karşı daha duyarlı olabileceğine işaret etmektedir. Nitekim uluslararası çalışmalar da, HPV tanısı alan kadınların doğurganlık ve gebeliğe ilişkin kaygılarının özellikle çocuk sahibi olma yaşına yaklaşıldığında daha belirginleştiğini bildirmektedir (11). Evli kadınlarda gözlenen etkinin, HPV'nin cinsel yolla bulaşan bir enfeksiyon olmasının ilişki dinamiklerine yansımasıyla ilişkili olabileceğine işaret etmektedir. Literatürde, evli HPV-pozitif kadınların tanı sonrası eşe yönelik güvensizlik, kızgınlık veya suçluluk duyguları yaşayabildiği; enfeksiyon için partnerini sorumlu tutabildiği belirtilmektedir (12). Dolayısıyla evlilik içinde edinilen bir HPV tanısı, tıbbi bir bulgunun ötesine geçerek çift iletişimini ve karşılıklı güveni etkileyebilir ve gebelik planlamasını karmaşıklaştırabilir. Öte yandan, bekâr ya da çocuk planı daha uzak olan kadınların kararlarının HPV tanısından daha az etkilendiği; bunun, yakın dönemde gebelik düşünmeme ya da HPV durumunu gizleme gibi davranışlarla ilişki olabileceği değerlendirilebilir.

Eğitim düzeyine ilişkin bulgular da dikkat çekicidir. Ortaöğretim mezunu kadınlarda gebelik planlarını HPV nedeniyle erteleme olasılığının daha yüksek olması, sağlık okuryazarlığı ve HPV'ye ilişkin bilgi düzeyinin etkisini düşündürmektedir. Daha düşük eğitim düzeyinde yanlış bilgi ve inanışların daha yaygın olabileceği; HPV pozitifliğinin gebelik açısından ''engel" olarak algılanabileceği öngörülebilir. Gebe hastalarla yapılan bir çalışmada, katılımcıların yalnızca %34,6'sının HPV hakkında yeterli bilgiye sahip olduğu bildirilmiştir (13). Benzer şekilde, eğitim süresi arttıkça HPV farkındalığının yükseldiği pek çok araştırmada gösterilmiştir. Bu nedenle, çalışmamızdaki ortaöğretim mezunu kadınların, yanlış/eksik bilgi nedeniyle, HPV'yi gebelik için olduğundan daha büyük bir tehdit olarak algılamaları olasıdır. Bulgular, sağlık hizmetlerinde HPV konusunda hedeflenmiş eğitim ve danışmanlığın gerekliliğini desteklemektedir.

Gebelik planlarını etkileyen başlıca faktörler arasında, virüsün bebeğe bulaşma olasılığına yönelik korku ön plana çıkmaktadır. Çalışmamızda kadınların önemli bir bölümü, HPV'nin gebelik sürecinde veya doğum sırasında bebeğe geçip geçmeyeceğine ilişkin kaygı bildirmiştir. Literatürdeki benzer araştırmalar da bu bulgularımızı destekler nitelikte olup, HPV pozitif kadınlarda benzer enfeksiyon geçişi endişelerinin yaygın olduğunu göstermektedir (11). Ancak, bu korku, mevcut kanıtlar ışığında değerlendirildiğinde çoğu durumda orantısız görünmektedir. Bulgular, anneden bebeğe vertikal geçişinin mümkün ancak görece nadir olduğunu göstermektedir. Yakın tarihli bir prospektif çalışmada, HPV pozitif annelerden doğan bebeklerde virüs saptanma oranının genel olarak %10'un altında olduğu; sezaryen ile doğumda bu oranın yaklaşık %3–4'e, vajinal doğumda ise yaklaşık %10'a kadar değişebildiği bildirilmiştir (14). Dahası, vertikal bulaş oluşsa dahi yenidoğanların çoğunun enfeksiyonu birkaç ay içinde bağışıklık sistemiyle temizlediği ve uzun vadeli ciddi bir sağlık sorunu yaşamadığı belirtilmektedir (15). Bu nedenle, bebeğe bulaşma riskine ilişkin kaygıların sağlık profesyonellerince doğru bilgilerle ele alınması kritik önem taşır. Aksi halde, abartılı risk algısı, gebelikten tümüyle vazgeçme ya da yalnızca HPV pozitifliği gerekçesiyle sezaryen talebi gibi gereksiz müdahale isteklerine yol açabilmektedir.

Çalışmamız, HPV tanısının öz-algı üzerindeki olumsuz etkilerine de işaret etmektedir. Özgüven kaybı ve damgalanma hissi, HPV pozitifliğinin sık bildirilen psikososyal sonuçları arasındadır (12). Farklı kültürlerde yapılan çalışmalar, HPV testi pozitif gelen kadınların "kirlenmiş" ya da "ayıplı" hissetme eğiliminde olduklarını; utanma ve değersizlik duyguları yaşayabildiklerini göstermektedir (16). McCaffery ve ark.'nın çalışmasında, HPV pozitif kadınların önemli bir kısmı test sonucunu öğrendikten sonra cinsel ilişkileri hakkında olumsuz düşünceler geliştirmiş; bir kısmı kendini "kirli"

veya "ucuz" hissettiğini ifade etmiştir (16). Benzer şekilde İran'da yapılan bir araştırmada kadınların kendilerini "çirkin, cüzamlı, iğrenç" gibi ifadelerle tanımladıkları bildirilmiştir (12). Bu bulgular, HPV enfeksiyonunun biyolojik etkilerinin ötesinde güçlü bir sosyal ve psikolojik yük oluşturduğunu ortaya koymaktadır. Sonuç olarak, bazı kadınlar yalnızca sağlık kaygısıyla değil, toplumsal yargılanma ve eş nezdindeki değer algısındaki sarsılmayla da gebelik kararlarını erteleyebilmektedirler.

Çalışmamızda HPV'ye ilişkin bilgi düzeyi ve inanışların büyük çoğunluğunun gebelik planlaması üzerinde anlamlı bir etkisi saptanmamıştır. Bununla birlikte bir kısmı "HPV'nin bebeğe bulaşabileceği" ya da "gebeliği doğrudan etkileyebileceği" yönündeki inançlar kararları istatistiksel olarak anlamlı biçimde etkilemiştir. Yanlış/eksik bilginin bireysel risk algısını artırabileceği ve literatürde de bildirildiği üzere hatalı inanışlara (örneğin HPV'nin her zaman kanserle sonuçlanacağı ya da aşının gebelikte zararlı olduğu gibi) zemin hazırlayabileceği göz önünde bulundurulmalıdır. İran'da HPV pozitif kadınlarla yapılan bir çalışmada, katılımcıların bir kısmı anormal Pap-smear sonucu varken gebeliğin durumu kötüleştireceğinden endişe ettiği; önemli bir kısmının da HPV aşısının gebelik ve emzirme dönemindeki güvenliğine ilişkin bilgisizlik yaşadığı bildirilmiştir (11). Psikososyal değişkenlerle gebelik planlaması arasında çalışmamızda doğrudan ilişki saptanmamış olsa da, katılımcıların %46,6'sının tanı sonrası belirgin psikolojik zorlanma yaşadığını belirtmesi önemlidir. HPV pozitifliği bir sonucun kısa vadede kaygıyı artırdığı iyi bilinmektedir (17,18). Tarama çalışmalarında, HPV testinin pozitif gelmesinin rutin smear testine kıyasla daha fazla endişe ve stres yarattığı; ancak bu etkinin zamanla azalma eğiliminde olduğu gösterilmiştir. Örneğin, Birleşik Krallık'ta yapılan bir araştırmada HPV testi pozitif ancak henüz prekanseröz lezyonu olmayan kadınların anksiyete skorları tanı sonrası belirgin artmış; 6-12 ay içinde büyük ölçüde gerilemiştir (19). Bununla birlikte, psikososyal etkinin tamamen ortadan kalkmadığı; Hong Kong'da kolposkopi izlemi altındaki HPV testi pozitif kadınlarda 6 ay sonunda "psikososyal yük" skorunun HPV negatif kontrollere kıyasla hâlâ daha yüksek olduğu saptanmıştır (20). Bu nedenle, tanı anındaki destek kadar izlem sürecinde psikolojik iyilik hâlinin değerlendirilmesi ve gerektiğinde müdahale edilmesi önem taşır.

Bulgularımız, kadın sağlığı, danışmanlık hizmetleri ve sağlık eğitimi boyutlarında çeşitli uygulamalara ihtiyaç olduğunu ortaya koymaktadır. Uygulama açısından, bulgular kadın sağlığı, danışmanlık ve sağlık eğitimi boyutlarında çok bileşenli girişimlere ihtiyaç olduğunu göstermektedir. Gebelik planlama sürecindeki kaygılar sağlık profesyonellerince etkin biçimde ele alınmalı; HPV'nin gebelik seyrine etkilerine ilişkin güncel, kanıta dayalı bilgilerle yanlış inanışlar düzeltilmelidir. HPV enfeksiyonunun çoğu durumda gebelik sonuçlarını olumsuz etkilemediği, tek başına düşük/erken doğum nedeni olarak görülmediği ve vertikal bulaş olasılığının düşük olduğu açıkça anlatılmalıdır. Danışmanlık hizmetlerine psikososyal destek entegre edilmelidir. Gerekli durumlarda psikologlar veya psikiyatri hemşireleri multidisipliner ekibe dahil edilerek özgüven kaybı, utanç ve kaygı ile baş etme desteklenmelidir. Nitekim yakın tarihli bir randomize kontrollü çalışmada, HPV testi pozitif kadınlara uygulanan yapılandırılmış motivasyonel danışmanlığın anksiyete ve depresyon düzeylerini anlamlı biçimde azalttığı gösterilmiştir (21). Toplum düzeyinde, damgalamayı azaltmaya ve yanlış bilgileri düzeltmeye yönelik halk sağlığı programları yürütülmelidir. Okul temelli eğitim ve medya kampanyalarıyla HPV'nin yaygın bir enfeksiyon olduğu; uygun tarama ve aşılama ile ciddi sonuçların önlenebileceği vurgulanmalıdır. Aşılama oranlarının artırılması, hem enfeksiyon sıklığını azaltacak hem de korkuları daha yönetilebilir kılacaktır.

Genel olarak bulgularımız, uluslararası literatürle uyumlu biçimde, HPV testi pozitif kadınların gebelik planlamasında karşılaştıkları güçlüklerin çok boyutlu ele alınması gerektiğini göstermektedir. Kadınların yalnızca tıbbi tedaviye değil; doğru bilgiye, psikolojik desteğe ve yargılayıcı tutumlardan arındırılmış bir bakım ortamına gereksinimi vardır. Sağlık politikaları ve klinik uygulamalar, HPV pozitif kadınlara üreme planları konusunda kapsamlı, standart ve kanıta dayalı danışmanlık sunarak bebeğe bulaşma korkusu, özgüven kaybı ve bilgi eksikliği gibi engelleri azaltmayı hedeflemelidir.

SONUÇ

Bu çalışma, HPV pozitifliğin özellikle 25–34 yaş, evli ve ortaöğretim düzeyindeki kadınlarda gebelik planlarını etkileyebildiğini; buna karşılık bilgi/algı göstergelerinin topluca ele alındığında tek başına belirleyici olmadığını ortaya koymaktadır. Klinik danışmanlıkta, vertikal bulaş riskinin düşük olduğuna ve enfeksiyonların çoğunun kendiliğinden temizlenebildiğine ilişkin kanıta dayalı mesajların psikososyal destekle birlikte sunulması önerilir.

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Sedoanalgesia and Colposcopy: A Retrospective Comparison of Procedural Outcomes

Sedoanaljezi ve Kolposkopi: İşlemsel Sonuçların Retrospektif Karşılaştırması

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ABSTRACT

Aim: To evaluate the effect of sedoanalgesia on procedural outcomes of colposcopy, with particular emphasis on procedure time and the need for hemostatic interventions.

Materials and Methods: This retrospective cohort study included women aged 25–65 years who underwent colposcopic biopsy between February and October 2024. Patients were allocated to either a sedoanalgesia group or a no-anesthesia group based on clinical indications and patient preference. The primary outcome was colposcopy table time, defined as the interval from patient positioning to completion of hemostasis. Secondary outcomes included the need for cauterization and additional hemostatic measures.

Results: A total of 191 patients were analyzed (80 with sedoanalgesia, 111 without). The mean colposcopy table time was significantly shorter in the sedoanalgesia group. Cauterization was required in 8.8% of sedated cases compared with 46.8% of non-sedated cases (p<0.001). The requirement for tranexamic acid sponges was also markedly lower in the sedoanalgesia group. No anesthesia-related complications were observed.

Conclusions: Sedoanalgesia during colposcopy was associated with shorter procedure time and reduced need for cauterization. These findings suggest potential clinical and occupational benefits, supporting the selective use of sedoanalgesia in colposcopy. Prospective studies are needed to confirm these results.

Keywords: Electrocautery, colposcopy, sedoanalgesia

ÖZ

Amaç: Bu çalışmada sedoanaljezi ile yapılan kolposkopi işleminin sonuçlar üzerine etkisi değerlendirildi. Özellikle işlem süresi ve hemostaz gereksinimi üzerindeki etkiler incelendi.

Gereç ve Yöntemler: Bu retrospektif çalışmamıza, 2 Şubat 2024 ile 2 Ekim 2024 tarihleri arasında kolposkopik biyopsi yapılan ve yaşları 25 ile 65 arasında değişen olgular dahil edildi. Hastalar klinik özellikler ve hasta tercihi doğrultusunda sedoanaljezi grubu ve anestezisiz grup olmak üzere ikiye ayrıldı. Birincil sonlanım noktası, hastanın masaya alınmasından biyopsi sonrası hemostazın sağlanmasına kadar geçen süre olarak tanımlanan kolposkopi masa süresi idi. İkincil sonlanım noktaları ise koter gereksinimi, traneksamik asit emdirilmiş sünger kullanımı ve anestezi ile ilişkili komplikasyonlardı.

Bulgular: Toplam 191 hasta analiz edildi (80 sedoanaljezi, 111 anestezisiz). Ortalama kolposkopi masa süresi sedoanaljezi grubunda anlamlı olarak daha kısa bulundu (p<0,001). Koter gereksinimi sedoanaljezi grubunda %8.8, anestezisiz grupta ise %46.8 idi (p<0,001). Traneksamik asit süngeri kullanımı da sedoanaljezi grubunda belirgin şekilde daha düşüktü. Çalışma süresince herhangi bir anestezi ile ilişkili komplikasyon gözlenmedi.

Sonuç: Sedoanaljezi ile yapılan kolposkopilerde işlem süresi daha kısa, koter ihtiyacı ise daha az bulunmuştur. Bu sonuçlar sedoanaljezinin yalnızca hasta konforunu artırmakla kalmayıp aynı zamanda işlemin etkinliğini ve güvenliğini de destekleyebileceğini düşündürmektedir. Bulgularımız klinik uygulamada sedoanaljezinin seçilmiş hastalarda kullanılmasını desteklemekte olup, çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Koter, kolposkopi, sedoanaljezi

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INTRODUCTION

Cervical cancer remains one of the most common malignancies among women worldwide and continues to be a major public health concern, particularly in low and middle income countries. According to GLOBOCAN 2022 estimates, approximately 662300 new cases of cervical cancer and 348900 related deaths were reported globally in 2022 (1). Despite advances in screening and vaccination, the disease burden remains high, emphasizing the importance of accurate diagnosis and timely management. Colposcopy is an indispensable diagnostic and therapeutic tool in the evaluation of women with abnormal cervical cytology or high risk human papillomavirus positivity. The procedure allows for direct visualization of the cervix, targeted biopsy, and when necessary, minor therapeutic interventions. Although colposcopy is generally well tolerated, pain and anxiety during the procedure may compromise both patient compliance and the adequacy of the examination (2,3). Pain perception during colposcopy varies widely among patients and can negatively influence both the diagnostic yield and patient compliance. Several strategies have been proposed to improve tolerability, including local anesthetic agents, oral analgesics, and various sedation protocols (4,5). Sedoanalgesia, which combines anxiolysis and analgesia without the need for endotracheal intubation, has gained popularity in outpatient gynecologic procedures due to its favorable safety profile and rapid recovery (6,7). Nevertheless, evidence regarding the influence of sedoanalgesia on key colposcopic outcomes, including procedure duration and the requirement for hemostatic interventions, is still scarce.

The aim of this study was to compare colposcopies performed with and without sedoanalgesia in terms of procedural outcomes. Specifically, we sought to evaluate the effect of sedoanalgesia on colposcopy table time, the need for cauterization, and additional hemostatic measures in a retrospective cohort of women undergoing colposcopic biopsy.

METHODS

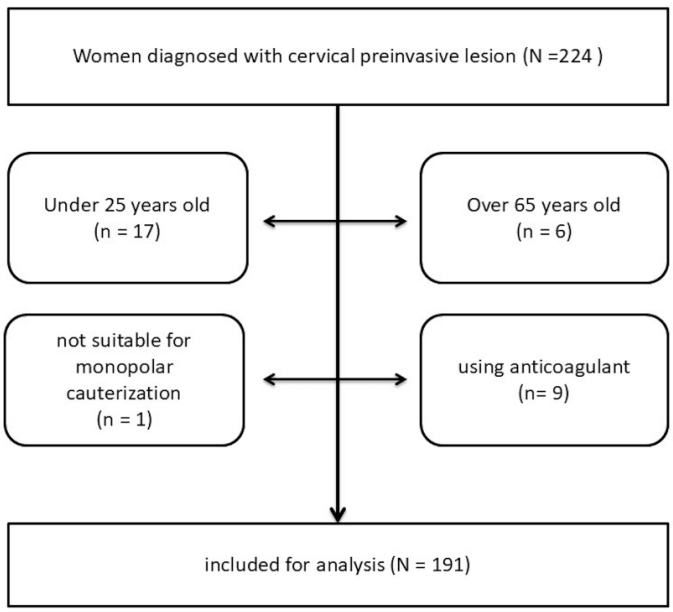
Patient Selection and Study Design

This retrospective cohort study was conducted at Afyonkarahisar State Hospital, a tertiary referral center for gynecologic oncology, and included all consecutive women who underwent colposcopic biopsy between February 2, 2024, and October 2, 2024. Eligible patients were between 25 and 65 years of age. Exclusion criteria were therapeutic anticoagulation, age outside the specified range, and unsuitability for monopolar cauterization. After applying these criteria, a total of 191 patients were included in the analysis. Patients were allocated to one of two groups according to clinical characteristics and patient preference. Sedoanalgesia was offered to women with marked anxiety, vaginismus, a history of poor tolerance of previous pelvic examinations, or explicit request for sedation after preprocedural counseling. Women without these features underwent standard colposcopy without anesthesia. All procedures were performed consecutively, and no eligible patient within the study period was excluded except for the predefined criteria.

Procedural Technique

All procedures were performed in a dedicated outpatient colposcopy unit under standardized conditions. Patients were placed in the lithotomy position, and a bivalve speculum was introduced to allow full visualization of the cervix. Application of 5% acetic acid and Lugol's iodine was performed according to international colposcopy standards. Directed biopsies were obtained from all colposcopically suspicious areas. Endocervical curettage was performed when the squamocolumnar junction could not be fully visualized. The primary procedural time variable was defined as colposcopy table time. This interval started when the patient was positioned on the examination table and ended once complete hemostasis was achieved following the biopsy. Anesthesia induction and recovery durations were not recorded in a standardized manner and were therefore not included in the analysis. These parameters are acknowledged as limitations of the present study.

In the sedoanalgesia group, all patients were managed by an anesthesiology team. Intravenous midazolam (0.03–0.05 mg/kg) and fentanyl (1–2 µg/kg) were administered to provide conscious sedation and analgesia. Supplemental oxygen was delivered via nasal cannula at 2–3 L/min. Continuous monitoring of oxygen



saturation, heart rate, blood pressure, and respiratory rate was maintained throughout the procedure. Sedation depth was titrated to allow patient comfort while maintaining spontaneous ventilation. Following the procedure, all sedated patients were observed in a recovery unit until they met standardized discharge criteria, including stable vital signs and complete orientation. Any anesthesia-related adverse events, such as hypoxemia, airway obstruction, or need for additional intervention, were prospectively recorded.

Hemostasis after biopsy was achieved according to a predefined stepwise protocol. Initially, firm compression with a sterile gauze pad was applied for at least 60 seconds. If bleeding persisted, monopolar cauterization at standardized coagulation settings was used. In cases of refractory bleeding, a tranexamic acid–soaked vaginal sponge was inserted and left in place for 4–6 hours before re-evaluation. This hemostatic algorithm was consistently applied in both sedoanalgesia and no-anesthesia groups. To minimize inter-operator variability, all procedures were performed by a single gynecologic oncologist with more than ten years of colposcopy experience. The same operator was responsible for patient counseling, biopsy technique, and hemostatic measures, ensuring methodological consistency across the study cohort.

Outcome Measures and Statistical Analysis

The primary outcome measure of this study was colposcopy table time, defined as the interval from patient positioning on the examination table to completion of hemostasis following biopsy. Secondary outcome measures included the need for cauterization, the requirement for tranexamic acid–soaked sponge placement, and anesthesia related adverse events. Baseline patient characteristics such as age, referral indication, and histopathological findings were also recorded and compared between groups.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables were expressed as frequencies and percentages. Group comparisons for continuous variables were performed using the Student t test or the Mann Whitney U test, as appropriate. Categorical variables were compared using the chi square test or Fisher's exact test when expected frequencies were below five. A two sided p value less than 0.05 was considered statistically significant.

RESULTS

A total of 191 patients were included in the analysis, of whom 80 underwent colposcopy under sedoanalgesia and 111 without anesthesia. Baseline demographic and clinical characteristics of the two groups are presented in Table 1. The mean age did not differ

Table 1. Clinicopathologic characteristics and procedural outcomes of patients undergoing colposcopy (N = 191)

	Sedoanalgesia (n = 80)	No anesthesia (n = 111)	*p* value
Age, years, mean ± SD	33.7 ± 7.8	38.4 ± 8.7	-
Indication for colposcopy			
HPV type 16	37	42	
HPV type 18	7	10	
HPV type 16 and 18	7	8	
Other high risk HPV persiste	7	10	
Abnormal cervical smear	22	41	
HSIL	2	3	-
LSIL	12	22	
ASC-US	6	14	
ASC-H	1	2	
AGC	1	0	
Final histopathology			
CIN1	18	18	
CIN2	9	1	
CIN3	2	4	
Squamous cell carcinoma	1	0	
Chronic cervicitis	10	19	-
Cervical polyp	2	1	
Metaplasia	16	10	
Normal	23	57	
Inadequate/inappropriate	1	1	
Procedural outcomes			
Colposcopy table time, min, mean ± SD	10.2 ± 2.5	12.41 ± 1.5	**< 0.001***
Need for cauterization, n (%)	7	52	**< 0.001***
Need for tranexamic acid sponge, n (%)	1	8	0.94

significantly between groups. The distribution of referral indications, including high risk human papillomavirus positivity and abnormal cytology, was comparable between groups. Among patients referred due to abnormal cytology, the frequencies of HSIL, LSIL, ASC US, ASC H, and AGC are detailed in Table 1. The mean colposcopy table time was significantly shorter in the sedoanalgesia group compared with the no anesthesia group ($p<0.001$). Cauterization was required in 8.8% of cases in the sedoanalgesia group versus 46.8% in the no anesthesia group ($p<0.001$). The requirement for tranexamic acid–soaked sponges was also significantly lower among patients who received sedoanalgesia. Final histopathological diagnoses are summarized in Table 1. The distributions of cervical intraepithelial neoplasia grades and benign findings did not differ significantly between groups. No anesthesia related complications, including hypoxemia or airway intervention, were observed during the study period.

DISCUSSION

In this retrospective study, we compared procedural outcomes of colposcopies performed with and without sedoanalgesia. The main findings were that colposcopy table time was significantly shorter and the need for cauterization markedly reduced among patients receiving sedoanalgesia. The requirement for additional hemostatic measures such as tranexamic acid sponge placement was also lower in the sedoanalgesia group. Importantly, no anesthesia related complications were observed. These results suggest that sedoanalgesia may not only improve patient comfort but also contribute to more efficient procedures with less reliance on electrocautery.

Previous studies have mainly focused on the role of sedoanalgesia in improving patient tolerance during colposcopy, often highlighting reduced pain perception and anxiety (7,8). Several reports have confirmed that sedoanalgesia improves pain scores and patient cooperation during colposcopic examination (8,9). Our findings are consistent with these studies in demonstrating favorable procedural outcomes. Prior investigations also suggested that reduced anxiety under sedation contributes to better visualization and more complete biopsies (10). This aligns with our observation of shorter procedure times in the sedoanalgesia group. Although previous research primarily emphasized patient comfort, some studies indirectly indicated lower intervention requirements under sedation (11,12). Our study expands on this evidence by directly quantifying cauterization rates and demonstrating a significant reduction with sedoanalgesia. By showing that sedoanalgesia facilitates faster procedures with fewer hemostatic interventions, our study provides pragmatic evidence that may guide clinical practice beyond patient comfort alone.

The present study has several limitations that should be acknowledged. First, its retrospective and single center design inherently restricts the generalizability of the results. Second, although colposcopy table time was clearly defined, anesthesia induction time, recovery duration, and total room occupancy time were not recorded, limiting a more comprehensive assessment of procedural efficiency. Third, allocation to sedoanalgesia or no anesthesia was influenced by clinical characteristics and patient preference, which may introduce selection bias despite the use of consecutive sampling. Finally, long term outcomes such as postoperative pain, delayed bleeding, or patient reported satisfaction were not systematically evaluated. These factors should be considered when interpreting the findings. Despite these limitations, our findings have practical implications for daily colposcopy practice. By reducing the need for cauterization, sedoanalgesia may minimize surgical smoke exposure and thereby improve the safety of both patients and healthcare providers. The shorter procedure time observed in the sedoanalgesia group also suggests potential benefits in terms of workflow efficiency in high volume outpatient settings. These results highlight sedoanalgesia not only as a tool for patient comfort but also as a strategy that may enhance procedural quality. Prospective multicenter studies with standardized anesthesia protocols and long term outcome measures are warranted to confirm these results and to further clarify the role of sedoanalgesia in colposcopic practice.

CONCLUSION

Sedoanalgesia during colposcopy was associated with shorter procedure time and a significantly reduced need for cauterization compared with standard practice. These findings suggest that sedoanalgesia may not only improve patient comfort but also enhance procedural efficiency and safety by minimizing the use of electrocautery and reducing surgical smoke exposure. While the results provide pragmatic evidence to support the selective use of sedoanalgesia in clinical practice, prospective multicenter studies with standardized protocols are required to confirm these observations and to better define its role in colposcopic management.

Ethics Approval and Consent to Participate: The present study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University Hospital (grant no: 2024/9 – 01.11.2024) and the research was continued in accordance with the Declaration of Helsinki. Consent was obtained from all patients during their hospitalization.

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Author Contributions: CYO: Conception and design, analysis of data, acquisition of data, drafting of the manuscript, writing the article; HE: Analysis of data, writing the article; NC: Participated in drafting, analysis and interpretation of data; SAS: Technical and material support, acquisition of data, participated in drafting; BM: Analysis of data, participated in drafting; DTA: Critical revision of the manuscript, Control/supervision. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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