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Evaluation of Obstetric Outcomes in Women with Endometriosis

Endometriozisli Kadınlarda Obstetrik Sonuçların Değerlendirilmesi

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ABSTRACT

Objective: It is generally accepted that the endometrium of women with endometriosis is abnormal, although there is ongoing debate as to whether these abnormalities impair decidualization and placentation during pregnancy. The aim of this study is to evaluate the obstetric and neonatal outcomes in patients diagnosed with endometriosis. **Material and Methods:** 1015 patients who underwent pregnancy follow-up in our obstetrics clinic and gave birth in our hospital between 2018 and 2023 were retrospectively examined. The patients evaluated in the study were evaluated in two separate groups according to the presence of endometriosis. The presence of preterm delivery, gestational diabetes (GDM), gestational hypertension (GHT), preeclampsia, premature rupture of membranes (PROM), fetal growth restriction (FGR), Neonatal Intensive Care Unit (NICU) were evaluated in all patients. **Results:** ART presence was found to be significantly higher in the endometriosis group (p=0.038). Gestational week was found to be significantly lower in the endometriosis group (p=0.018).The GHT presence was found to be significantly higher in the endometriosis group (p=0.034). The Cesarean presence was found to be significantly higher in the endometriosis group (p=0.037). Estimated blood loss volume was significantly higher in the endometriosis group (p=0.042). The NICU rate was significantly higher in the endometriosis group (p=0.044). **Conclusion:** Perinatal and neonatal outcomes resulting from endometriosis depend on multifactorial factors. Prospective and large population-based studies or meta-analyses are needed to clarify possible risks.

Keywords: Endometriosis; neonatal; perinatal

ÖZET

Amaç: Endometriozisli kadınların endometriumunun anormal olduğu genel olarak kabul edilmektedir, ancak bu anormalliklerin gebelik sırasında desidualizasyon ve plasentasyona zarar verip vermediği konusunda tartışmalar devam etmektedir. Bu çalışmanın amacı endometriozis tanısı almış hastalarda obstetrik ve neonatal sonuçları değerlendirmektir. **Gereç ve Yöntemler:** 2018-2023 yılları arasında kadın doğum kliniğimizde gebelik takibi yapılan ve hastanemizde doğum yapan 1015 hasta retrospektif olarak incelendi. Çalışmada değerlendirilen hastalar endometriozis varlığına göre iki ayrı grupta değerlendirildi. Tüm hastalarda preterm doğum, gestasyonel diyabet (GDM), gestasyonel hipertansiyon (GHT), preeklampsi, erken membran rüptürü (PROM), fetal büyüme kısıtlaması (FGR), Yenidoğan Yoğun Bakım Ünitesi (NICU) varlığı değerlendirildi. **Bulgular:** ART öyküsü endometriozis grubunda anlamlı olarak daha yüksek saptandı (p=0.038). Gebelik haftasının endometriozis grubunda anlamlı olarak daha düşük olduğu görüldü (p=0.018). GHT oranı endometriozis grubunda anlamlı olarak daha yüksek saptandı (p=0.034). Sezaryen oranı endometriozis grubunda anlamlı olarak daha yüksek saptandı (p=0.037). Tahmini kan kaybı hacmi endometriozis grubunda anlamlı olarak daha yüksek saptandı (p=0.042). NICU oranı endometriozis grubunda anlamlı olarak daha yüksek saptandı (p=0.044). **Sonuç:** Endometriozis kaynaklı perinatal ve neonatal sonuçlar multifaktöriyel faktörlere bağlıdır. Olası riskleri açıklığa kavuşturmak için prospektif ve geniş popülasyon tabanlı çalışmalara veya meta-analizlere ihtiyaç vardır.

Anahtar Kelimeler: Endometriozis; neonatal; perinatal

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Endometriosis is a chronic inflammatory disease defined as the presence of endometrial-like tissue outside the uterine cavity, and common symptoms include dysmenorrhea, dyspareunia, and subfertility.[1-3] Endometriosis is considered a benign gynecological disease that affects 10% of women of reproductive age throughout their lives and has an increasing incidence.[4] The prevalence of deep and ovarian endometriosis in pregnancy is approximately 5%, which is similar to the prevalence in women attending a general gynecology clinic, and approximately 50% of women are unaware that they have the condition.[5,6] It is generally accepted that the endometrium of women with endometriosis is abnormal, but there is ongoing debate as to whether these abnormalities impair decidualization and placentation during pregnancy.[7,8] Since these processes may be critical for pregnancy implantation and development, it has been hypothesized that pregnancy outcome in women with endometriosis may be affected.[9] Epidemiological studies have shown that women with some types of endometriosis may have an increased risk of preterm delivery and small for gestational age (SGA). The reason for this is changes in endometrial functions and prostaglandin (PG) levels.[10,11] Studies on the relationship between endometriosis and pregnancy outcome are contradictory. While literature reports an increased risk of preterm delivery, preeclampsia, and prenatal hemorrhage/placental complications, some studies have not found a relationship.[12-16] Previous studies reporting on obstetric complications in women with endometriosis have been based on fertility populations, retrospective data, or national statistics; the true complication rate in women with endometriosis is unknown.[17-20] The aim of this study is to evaluate the obstetric and neonatal outcomes in patients diagnosed with endometriosis.

MATERIALS AND METHODS

In present study was designed as a retrospective cohort study. The study was designed according to the Helsinki Declaration and informed consent forms were obtained from all patients. The study was initiated after receiving ethics committee approval numbered 24/26-6 from the hospital ethics committee. 1015 patients who underwent pregnancy follow-up in our obstetrics clinic and gave birth between 2018 and 2023 were retrospectively examined. The patients evaluated in the study were evaluated in two separate groups according to the presence of endometriosis. Pelvic or transvaginal ultrasonography data of all patients were evaluated from the hospital database for the presence of congenital and acquired uterine pathologies, including adenomyosis, uterine fibroids, and congenital uterine anomalies in addition to endometriosis. The presence of adenomyosis was defined according to the morphological uterus sonographic assessment criteria.[21] Myomas were defined as well-defined masses with posterior shadowing and circumferential vascularity within or communicating with the myometrium of the deuterine body or cervix in the first trimester of pregnancy.[22] Congenital uterine anomalies were evaluated according to the current ASRM classification system.[23] Ultrasonography data of the anterior and posterior pelvic compartments were evaluated for the presence of bilateral adnexal endometrioma and deep endometriosis. The International Deep Endometriosis Analysis Group accepted the presence of endometriosis as histologically proven endometriosis by surgery or the presence of lesions on ultrasound.[24] The presence of type of delivery, preterm delivery, gestational diabetes (GDM), gestational hypertension (GHT), assisted reproductive technology (ART) preeclampsia, premature rupture of membranes (PROM), fetal growth restriction (FGR), Neonatal Intensive Care Unit (NICU) were evaluated in all patients. The American Diabetesi-Association Criteria were used to diagnose gestational diabetes.[25] In the diagnosis of GDM, fasting blood glucose value > 92 mg/dL, first hour blood glucose value > 180 mg/dL, second hour blood glucose value > 153 mg/dL were determined as criteria. Diagnosis was made if any of the current values were exceeded. In women with no known history of diabetes mellitus, a 75-g OGTT test is performed at 24-28 weeks to measure fasting, 1-hour and 2-hour plasma glucose. Fasting for >8 hours is recommended for optimal evaluation of OGTT results.[25]

GHT was diagnosed in accordance with the most recent American College of Obstetricians and Gynecologists bulletin.[26] The combination of hypertension and proteinuria is used for the diagnosis of preeclampsia. GHT is defined as blood pressure levels of at >140 mm Hg as systolic or at >90 mm Hg as diastolic in measurements taken four hours or longer > 20th week of pregnancy in a woman whose blood pressure values were previously normal. Severe hypertension is considered when blood pressure is at >160 mm Hg systolic or at >110 mm Hg diastolic. To diagnose preeclampsia, women with hypertension also require the presence of proteinuria, defined as at >300 mg in a 24-hour urine collection. GHT is diagnosed in patients who meet hypertension criteria for preeclampsia without proteinuria or serious additional problems.[26] The Delphi Criteria were used to diagnose FGR.[27] When considering the Delphi FGR criteria, two single parameters (abdominal circumference (AC) or EFW < 3%) can be taken into account. Alternatively, cumulative evaluation of 4 parameters has been suggested. In these criteria (EFW or AC < 10th percentile): AC or EFW exceeding the percentiles in growth charts by > two quartiles and cerebroplacental ratio <5% or UA-PI >95% were accepted.[27] The estimated volume of blood loss was measured by utilizing the pregnant women's height, weight, and prenatal and postnatal Hct values.[28] Blood transfusion indications were determined in terms of the vital signs, estimated blood loss volume, and postpartum Hb value <8 g/dL.[28]

STATISTICAL ANALYSIS

Statistical analysis was conducted by utilizing the SPSS 26.0 (IBM-Inc.-Chicago-IL-USA). The normality of the distribution was evaluated with the Kolmogrov-Smirnov Test. Mean±Standard Deviation (SD) was used for evaluating normally distributed data, and median (range) was used for non-normally distributed data. Number (n) and percentage (%) were used for evaluating categorical data. The Fisher's Exact were employed in the categorical data analysis. Logistic regression analysis was used to determine the presence of endometriosis and adverse perinatal and neonatal outcomes.

RESULTS

ART history was found to be 7.1% in the endometriosis group and 4.4% in the group without endometriosis, and was found to be significantly higher in the endometriosis group (0.038). The mean gestational age at delivery was 38+4 weeks in the endometriosis group and 39+3 weeks in the group without endometriosis, and was found to be significantly lower in the endometriosis group (p=0.018) (Table 1).

GHT rate was found to be 6.1% in the endometriosis group and 2.4% in the non-endometriosis group, and it was found to be significantly higher in the endometriosis group (p=0.034). C/S rate was found to be 46.6% in the endometriosis group and 38.5% in the non-endometriosis group, and it was

TABLE 1: Comparison of demographic and obstetric data of patients.

	Endometriosis (+) n=210	Endometriosis (-) n=805	
	median (min-max)		p
Age (year)	32 (20-42)	30 (18-44)	0.38
BMI (kg/m^2)	24.1(18.2-35.6)	24.5 (18.4-34.8)	0.44
Smoking, n (%)	20 (%9.5)	81 (%10.1)	0.28
Gravidity	1.8 (1-4)	1.9 (1-4)	0.66
Parity	1.6 (1-4)	1.7 (1-4)	0.56
Multiple pregnancy, n (%)	14(%6.6)	56(%6.9)	0.61
ART, n (%)	15 (%7.1)	36(%4.4)	0.038
Abortion, n (%)	16 (%7.6)	57 (%7)	0.34
Gestational week	38+4 (31-41)	39+3 (29-41)	0.018

BMI: Body mass index, ART: Assisted reproductive technology.

TABLE 2: Comparison of perinatal outcomes between groups

	Endometriosis (+) n=210	Endometriosis (-) n=805		
	n (%)		OR (%95 CI)	p
GHT	13 (%6.1)	20 (%2.4)	2.54 (1.22–8.08)	0.034
Preeclampsia	9 (%4.2)	17 (%2.1)	2.02(0.62–8.34)	0.26
GDM	18 (%8.5)	66 (%8.1)	1.05(0.54–2.22)	0.88
Vaginal birth	112 (%53.4)	495 (%61.5)	1.21(1.09–2.02)	0.037
C/S	98 (%46.6)	310 (%38.5)		
Preterm birth	14 (%6.6)	34 (%4.2)	1.57(0.92–3.92)	0.076
PROM	13 (%6.1)	35 (%4.3)	1.42(0.9–3.82)	0.088
FGR	12 (%5.7)	47 (%5.8)	0.98(0.88–3.54)	0.90
ΔHb	0.8±0.6	0.6±0.7	1.33(1.12–2.54)	0.14
Estimated blood loss volume (cc)	545 (210-870)	340 (120-650)	1.60(1.37–3.26)	0.042
Blood transfusion	16 (%7.8)	44 (%5.4)	1.44(1.18–2.96)	0.1

GHT: Gestational hypertension, GDM: Gestational diabetes mellitus, C/S: Cesarean section, PROM: Premature rupture of membranes, FGR: Fetal growth restriction, ΔHb: Preop-Postop difference

TABLE 3: Comparison of neonatal outcomes between groups.

	Endometriosis (+) n=210	Endometriosis (-) n=805		
	Mean±SD		OR (%95 CI)	p
Apgar (1st min)	8.2±0.8	7.8±0.7	1.05 (0.92–1.09)	0.11
Apgar (5th min)	8.7±1.1	8.3±0.9	1.04(0.90–1.16)	0.16
Birth weight (gr)	3070±580	3190±640	0.96(0.84–1.18)	0.66
NICU, n (%)	18 (%8.4)	31 (%3.8)	2.21(1.14–4.08)	0.044

NICU: Neonatal Intensive Care Unit

found to be significantly higher in the endometriosis group (p=0.037). The estimated blood loss volume level was 545 (210-870) cc in the endometriosis group and 340 (120-650) cc in the non-endometriosis group, and was significantly higher in the endometriosis group (p=0.042) (Table 2).

NICU rate was found to be 8.4% in the endometriosis group and 3.8% in the non-endometriosis group, and it was found to be significantly higher in the endometriosis group (p=0.044) (Table 3).

DISCUSSION

In present study showed that in the group with endometriosis, in terms of pregnancy outcomes, the GHT rate, C/S rate, NICU requirement and, estimated blood loss volume were significantly higher in the endometriosis group. Studies evaluating the perinatal and neonatal effects of endometriosis in the literature have presented results from a very broad perspective. We believe that these differences between the results are due to many factors such as patient selection, number of patients, diagnostic method of endometriosis, severity of endometriosis and study methodology. The relationship between endometriosis and preterm delivery is one of the perinatal complications that is particularly emphasized. It has been reported that the eutopic endometrium and the junctional zone are abnormal at the molecular and functional levels, leading to impaired endometrial growth, maturation and decidualization, endometrial receptivity, defective spiral artery remodeling, and defective deep placentation.[8,9] Defective arterial remodeling is associated with a

number of pregnancy complications, including preterm delivery, preeclampsia and FGR.[9,29] Abnormal placentation may increase the risk of placental complications during pregnancy. Endometriosis is also associated with a chronic pelvic inflammatory process, and increased levels of prostaglandins and cytokines have been documented in the peritoneal fluid of women with Endometriosis.[30-33] Increased levels of these proinflammatory mediators may stimulate myometrial contractions and cervical ripening, leading to preterm delivery.[12,34] In addition, the normal frequency and amplitude of uterine contractions are altered in women with endometriosis, which may affect embryo delivery and implantation.[35,36] Chronic inflammation may constitute the biochemical background for preterm delivery in women with endometriosis. A meta-analysis by Lalani et al. showed that the probability of preterm delivery is higher in women diagnosed with pelvic Endometriosis.[37] The meta-analysis by Breintoft et al. similarly showed that the probability of preterm delivery was higher in women diagnosed with pelvic endometriosis.[38] A study by Exacoustos et al. found a correlation between the endometriosis and preterm delivery.[39] The study by Farella et al. showed a higher prevalence of preterm delivery in women with a history of surgical treatment for endometriosis, especially in those with deep disease of the rectum or bladder.[40] A study on endometriosis and adverse obstetric outcomes based on more than 1.4 million births in Sweden found that endometriosis was associated with preterm delivery.[12] However, Aris, et al. reported in their study that women with endometriosis had no increased risk of preterm delivery.[41] Similarly, Mekaru, et al. found in their study that women with endometriosis had no increased risk of preterm delivery.[16] Although the preterm delivery rate was found to be higher in the endometriosis group, no statistically difference was found between the groups. Theories that may support excessive blood loss during cesarean section include a number of associations with angiogenesis, mild bleeding disorders, pelvic adhesions, surgical complexity, increased operative time, or bleeding from endometriotic foci.[42,43] Endometriotic lesions may be more prone to bleeding when disturbed during pregnancy and surgery.[43] Decidualization of endometriotic lesions is a hormonally induced phenomenon that women with endometriosis during pregnancy.[5] Stromal vascularity, immune cell influx, and edema from lesions may also contribute to intraoperative blood loss.[44,45] Some women who experience excessive intraperitoneal bleeding at ovulation are at increased risk of developing deep endometriosis, but if the bleeding disorder is clinically significant, we would also expect excessive blood loss during vaginal delivery.[46] In the study by Lafleur et al., active endometriosis was associated with an increased risk of severe hemorrhage, whereas inactive endometriosis was less strongly associated.[47] In the meta-analysis by Breintoft et al., no significant difference was observed in the frequency of postpartum bleeding in women diagnosed with endometriosis compared to women without endometriosis.[38] In our current study, while no significant difference was found between the groups in terms of the presence of massive bleeding requiring blood transfusion, the estimated blood loss volume level was found to be significantly higher in the endometriosis group. In the nationwide study by Stephansson et al., no association was observed between SGA and endometriosis.[12] Similarly, no association was found between endometriosis and SGA in the Danish cohort study by Glavind et al.[48] Fernando et al. suggested that women with endometrioma have an increased risk of SGA, but this risk is not present in women with other forms of endometriosis.[10] In our results, no significant difference was found in terms of FGR rate between the endometriosis group and the non-endometriosis group. The relationship between endometriosis and gestational hypertension and preeclampsia is another issue that has been emphasized in the literature, with conflicting results. In the study by Chen et al., no association was found between the presence of endometriosis and the risk of gestational hypertension.[49] In the study conducted by Farland et al., women with a history of laparoscopically confirmed endometriosis had a 30% higher risk of developing hypertensive disorders during pregnancy.[50] In the study by Hadfield et al., no evidence was found for an association between endometriosis and the risk of hy-

pertension or preeclampsia in pregnancy.[51] In our results, while the GHT rate was found to be significant in the endometriosis group compared to the non-endometriosis group, no difference was observed between the groups in terms of preeclampsia risk. The increased incidence of PROM in pregnancy in women with endometriosis is associated with a physical/microbial inflammatory process that weakens the fetal membranes and increases prostaglandins (PGs), which in turn lead to collagen degradation within the fetal membranes through the action of metalloproteinases (MMP-9) and collagenase.[52] Increased levels of PG and inflammatory cytokines in women with endometriosis locally activate MMP-9 and matrix-degrading enzymes and are responsible for the invasiveness of lesions.[31,53] In the study by Conti et al., the risk of PROM was significantly higher in primiparous women with endometriosis compared with the control group.[54] In the study by Harada et al., PROM was found to be significantly higher in Endometriosis group compared to non-endometriosis group who conceived naturally or received infertility treatment other than ART treatment.[32] Although our study revealed that the rate of PROM was higher in the endometriosis group, it did not detect a significant result. Pérez-López et al.'s meta-analysis stated that endometriosis had no significant effect on the risk of GDM.[55] The study by Salmeri et al. revealed an increased risk of GDM in endometriosis and with a possible progressive effect in more advanced stages of the disease.[56] In addition to the different results presented in the literature, our study did not detect a clear relationship between endometriosis and GDM in the data we obtained. This difference in the studies may be related to the way endometriosis is diagnosed and the degree to which the severity of endometriosis is different. In Lalani et al.'s meta-analysis, women with endometriosis were more likely to be admitted to the NICU.[37] Similarly, in the meta-analysis by Horton et al., it was reported that the probability of being admitted to the NICU was higher for women with Endometriosis.[57] Our current data are consistent with the literature results, and it has been concluded that NICU demand is significantly higher in the presence of endometriosis. In the evaluation of Breintoft et al., the cesarean ratio was found to be higher in the endometriosis group than in the control group.[38] Similarly, in present study, the cesarean ratio was found to be higher in the endometriosis group. The reason for this may be the decision to perform cesarean section due to the secondary outcome of perinatal complications. However, the general increase in our cesarean rates compared to the literature has become a public health issue that needs to be examined in depth. We consider our study as one of the rare cohort studies in our country that evaluates obstetric and neonatal outcomes for women with endometriosis on a large scale and multifactorially. Our study had a consistent methodology and considered the way patients conceived, and we believe this may have an independent effect on the outcomes of interest. In endometriosis, surgery and histology continue to be the gold standard diagnostic techniques internationally. Most of the patients in the endometriosis group were diagnosed with endometriosis before pregnancy, which can be considered as an advantage of this study. We accept, specifically in our study, that women in the endometriosis group diagnosed only by ultrasound did not receive surgical confirmation of endometriosis and that there may be cases of endometriosis that were misdiagnosed on ultrasound. The fact that endometriosis was not surgically confirmed in all patients in our study may be considered a limitation. However, laparoscopy is no longer accepted as a diagnostic reference standard for endometriosis and is now recommended only in women with persistent symptoms and negative imaging results or in those who have failed empirical treatment.[58] We acknowledge that we may have missed detecting endometriosis in some women in the group without endometriosis, particularly in women with peritoneal disease. Peritoneal endometriosis is common, not always detected on pelvic ultrasound, and may be found incidentally at laparoscopy.[59] It is clear that including only women with surgical diagnosis would be a more robust method for screening and defining disease subtypes. However, women with endometriosis are increasingly being treated conservatively, and including only those with surgical diagnosis would have limited the population studied

to women with symptomatic disease or those who elected surgery. There is a possibility that there were also women with mild and minimal endometriosis in the group of patients without endometriosis, and when evaluating the findings of our study, careful interpretation is necessary regarding women with mild and minimal disease.

CONCLUSION

Perinatal and neonatal outcomes resulting from endometriosis depend on multifactorial factors. We believe that the sample size in our study population may lead to associations that are not statistically significant and therefore prospective and large population-based studies or meta-analyses are needed to provide meaningful results and clarify possible risks.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ufuk Atlıhan, Selçuk Erkılıç;* ***Design:*** *Onur Yavuz;* ***Control/Supervision:*** *Ferruh Acet;* ***Data Collection and/or Processing:*** *Can Ata;* ***Analysis and/or Interpretation:*** *Tevfik Berk Bildacı;* ***Literature Review:*** *Ufuk Atlıhan;* ***Writing the Article:*** *Ufuk Atlıhan, Burak Ersak;* ***Critical Review:*** *Hüseyin Aytuğ Avşar.*

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