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Why the first pregnancy results with ectopic location? A retrospective analysis to identify the potential risk factors

Elif Kulahci Aslan[1], Anıl Erturk[2]

[1]*Department of Obstetrics and Gynecology, Bursa Private Acıbadem Hospital, Bursa, Türkiye*
[2]*Department of Obstetrics and Gynecology, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye*

ABSTRACT

Aim: To identify potential risk factors associated with ectopic pregnancy (EP) in healthy primigravid women.
Methods: This retrospective study was conducted at a tertiary research hospital, involving primigravid patients diagnosed with EP between 2016 and 2023. The control group comprised primigravid women with healthy term birth (HB). Demographic parameters, including age, body mass index (BMI), fertility status, menstrual pattern, systemic disease presence, surgical history, previous pelvic infection were documented and compared between two groups. Correlation and regression analyses were performed to determine significant factors linked to EP.
Results: A total of fifty primigravid women had EP, while the control group included fifty with HB. Women with EP had a significantly higher mean age compared to those with HB (26.5 ±5.2 vs. 21.5 ±2.3, $p<0.01$). The mean BMI was lower in women with EP compared to those with HB (23.8 ±4.1 vs. 25.9 ±2.5, $p<0.01$). Irregular menstrual patterns were more prevalent in the EP group than the HB group (28% vs. 12%, $p=0.04$). The EP group had a higher rate of previous abdominal surgery (8% vs. 2%, $p=0.04$). The regression analysis indicated that older age and lower BMI were significant risk factors associated with the presence of ectopic pregnancy.
Conclusions: EP poses a distressing situation for couples, and predicting the risk of such pregnancies remains challenging. This study highlights that higher age and lower BMI are primary risk factors for ectopic pregnancy in primigravid women.

Key words: Pregnancy, ectopic, risk factors, nulliparity, primigravid women, body mass index.

✉ *Dr. Elif Kulahci Aslan*
Department of Obstetrics and Gynecology, Bursa Private Acıbadem Hospital, Bursa, Türkiye
E-mail: elifklhc@hotmail.com
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Introduction

An ectopic pregnancy (EP), also referred to as an extrauterine pregnancy, occurs when the blastocyst implants outside the endometrial cavity [1]. Its description dates back to 963 AD when Albucasis first defined the condition [2]. EP constitutes approximately 1-2% of all pregnancies [3]. Among women presenting with first-trimester bleeding and pain in emergency settings, about 16% are diagnosed with EP [4]. For centuries, EP posed a mortal threat until advancements in diagnostic and therapeutic techniques such as pregnancy tests, ultrasound,

and laparoscopy [5-7]. Presently, the condition can be relatively easily diagnosed and treated. However, predicting and preventing EP remains a challenge.

Various established risk factors contribute to the development of EP, with higher risks associated with a history of previous EP, presence or history of intrauterine device use, pelvic inflammatory disease, and salpingitis isthmica nodosa [8-11]. Other factors linked to EP include chlamydia infection, infertility, multi-partnership, smoking, and maternal age below 18 or above 35 [12-14]. Despite the presence of numerous risk factors, EP can still occur in primigravid women without any identifiable risk factors.

The purpose of this study is to determine whether there are any specific risk factors for the development of EP among primigravid women.

Materials and methods

Study design & ethical approval

This retrospective cohort study was conducted at a tertiary research hospital over a ten-year period from 2016 to 2023. The study design received approval from the hospital's ethical committee with the reference number 2011-KAEK-25 / 2023/05-13.

Study population and data collection

The clinic's electronic database was thoroughly reviewed for cases spanning from 2016 to 2023. Specifically, reproductive-aged women (aged 18 to 45) diagnosed with EP were identified, and among them, primigravid women with EP were selected. Randomly chosen primigravid women (aged 18 to 45) who had experienced their first pregnancy without complications and had healthy full-term deliveries constituted the control group. Demographic parameters for both groups were extracted from the database, encompassing maternal age, body mass index (BMI) in kg/m², fertility status, menstrual pattern, presence of systemic diseases, surgical history, and any prior pelvic infections. To access the mentioned clinical and demographic data from the electronic database, we reviewed the mandatory pregnancy monitoring forms that contain demographic and clinical details, which are completed during the initial visit for each pregnancy. Moreover, we examined the discharge summaries of patients diagnosed with ectopic pregnancies who were hospitalized.

Patients who were not experiencing their first pregnancy and those with unclear data retrieval were excluded from the study. A total of 50 ectopic patients with comprehensive and accurate demographic data retrieved from the database were subjected to analysis. Similarly, the control group included 50 primigravid patients who had successfully completed healthy full-term deliveries within the defined timeframe, with complete and accessible demographic data.

Statistical analysis

Continuous variables were presented as either mean ± standard deviation (SD) or as median with the 25th-75th percentile, depending on their distribution. Categorical variables were expressed as percentages. To compare continuous variables between the groups, the independent samples t-test or Mann-Whitney U test was used, as appropriate. Categorical variables were compared using the Chi-square test and its derivatives. A two-sided p-value of 0.05 was considered statistically significant. Correlations between variables were explored using Spearman and Pearson correlation analyses. Additionally, binary logistic regression analysis was conducted to identify predictive factors for ectopic pregnancy among primigravid women.

Results

Over the period of 2016-2023, a total of 324 women were diagnosed with EP. Among them, 50 women were experiencing their first pregnancy and had accessible data. The treatment modalities for EP cases included methotrexate in 44% (22) of cases, laparoscopy in 8% (4) of cases, laparotomy in 14% (7) of cases, and endometrial sampling with a conservative approach in 34% (17) of cases.

As for the control group, 50 primigravid women who had a healthy term normal vaginal birth were blindly selected, independent of the EP group.

Comparison of parameters between the groups revealed significant differences. Women with EP had a notably higher mean age compared to those with healthy births (26.5 ± 5.2 vs. 21.5 ± 2.3, $p < 0.01$). Additionally, the mean BMI was lower in women with EP compared to those with healthy births (23.8 ± 4.1 vs. 25.9 ± 2.5, $p < 0.01$). Irregular menstrual patterns were more prevalent in the EP group than in the healthy birth group (28% vs. 12%, $p = 0.04$). Furthermore, the EP group had a higher rate of previous abdominal surgery (8% vs. 2%, $p = 0.04$) (Table-1).

Correlation analysis showed significant correlation between age, BMI, menstrual pattern and history or previous surgery. (Table-2)

Table 1. Demographic parameters of the groups.

Parameters	EP group (n=50)	HB group (n=50)	*p*
Age (yrs.)	26.1 ± 5.2	21.5 ± 2.3	*<0.01*
BMI (kg/m^2)	23.8 ± 4.1	25.9 ± 2.5	*<0.01*
Irregular Menstrual Pattern	14 (28)	6 (12)	*0.04*
Fertility Treatment	2 (4)	-	*0.15*
Previous Abdominal Surgery	4 (8)	1 (2)	*0.04*
Systemic Disease	7 (14)	4 (8)	*0.35*
PID history	-	-	*N/A*

Values: Mean ± SD or n (%). EP: ectopic pregnancy, HB: healthy birth, BMI: body mass index, PID: pelvic inflammatory disease.

Table 2. Correlation analysis of the significant risk factors.

Parameters		Age	BMI	Menstrual Pattern	Previous Surgery
Age	Correlation Coefficient	1.000	-.171	.113	.109
	Sig. (2-tailed)	.	.088	.261	.283
	N	100	100	100	99
BMI	Correlation Coefficient	-.171	1.000	.312**	-.275**
	Sig. (2-tailed)	.088	.	.002	.006
	N	100	100	100	99
Menstrual Pattern	Correlation Coefficient	.113	.312**	1.000	-.103
	Sig. (2-tailed)	.261	.002	.	.309
	N	100	100	100	99
Previous Surgery	Correlation Coefficient	.109	-.275**	-.103	1.000
	Sig. (2-tailed)	.283	.006	.309	.
	N	99	99	99	99
Ectopic Pregnancy	Correlation Coefficient	-.505**	.389**	-.200*	-.203*
	Sig. (2-tailed)	<.001	<.001	.046	.044
	N	100	100	100	99

Regression analysis indicated that older age and lower BMI were identified as significant risk factors associated with the presence of ectopic pregnancy (Table-3).

A Receiver Operating Characteristic (ROC) analysis was conducted to determine the threshold values for BMI and age in relation to the risk of ectopic pregnancy. The findings revealed that a BMI of 24.8 kg/m² was the critical parameter indicating a high risk of developing ectopic pregnancy, with an AUC of 0.72 ($p < 0.01$), 70% sensitivity, and 68% specificity. For women aged 25 years or older, the analysis indicated a risk for ectopic pregnancy with an AUC of 0.8 ($p < 0.01$), 65% sensitivity, and 88% specificity in their first pregnancy (Figure-1).

Table. 3 Regression analysis of the predictive factors of ectopic pregnancy.

Parameters	B	S.E.	Wald	*p*
Age	-.401	.099	16.262	*<0.01*
BMI	.360	.102	12.529	*<0.01*
Menstrual Pattern	2.993	.956	9.802	*.225*
Surgery History	20.440	17594.040	.000	*.999*
Constant	-22.487	17594.041	.000	*.999*

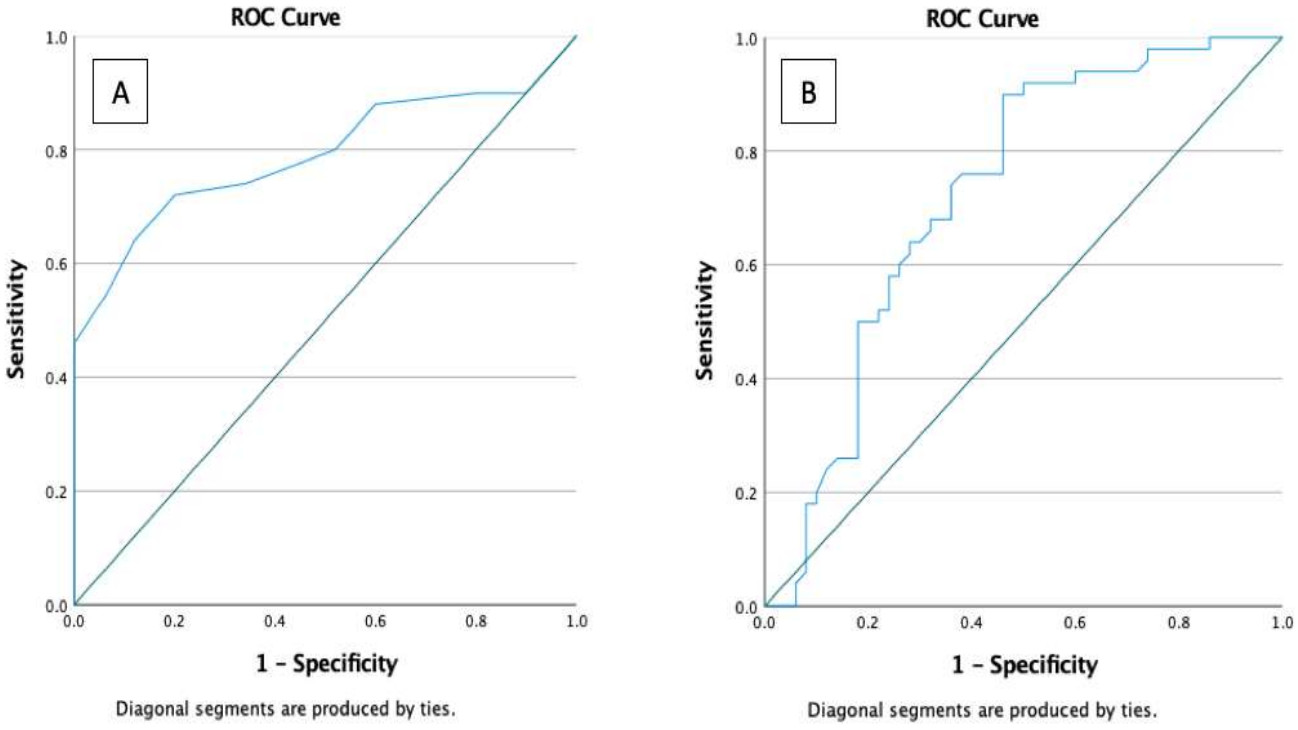

Figure 1. ROC Curves and Analyses for the Age and BMI. **A:** ROC curve for the women age (AUC: 0.8, $p<0.01$; CI: 0.69-0.89), threshold value to predict EP is 25 years with 65% sensitivity and 88% specificity. **B:** ROC curve for the BMI (AUC: 0.72, $p<0.01$; CI:0.62-0.82), threshold value to predict EP is 24.8 kg/m^2 with 70% sensitivity and 68% specificity.

Discussion

Despite numerous established risk factors, the precise cause of ectopic pregnancy remains unknown. Surprisingly, approximately 20% of ectopic pregnancy cases occur in primigravid women with no identifiable risk factors during their first pregnancy [15]. Our study findings indicate that low BMI and advanced maternal age are the primary risk factors associated with ectopic pregnancy development in primigravid women. Nevertheless, accurately predicting which women will experience ectopic pregnancy during their first pregnancy remains challenging. Nonetheless, these results could be valuable when considered alongside other high-risk factors in a combined approach.

A novel meta-analysis which aimed to elucidate the risk factors for ectopic pregnancy revealed that there is no strong evidence for risk factors according to published studies. As the result they concluded that chlamydia infection and smoking are graded as suggestive evidence. Also, intrauterine device and presence of endometriosis are graded as risk factors with weak evidence [16].

A well-designed study conducted in France aimed to identify the risk factors for developing ectopic pregnancy (EP) and arrived at conclusions similar to our own findings. Factors such as advanced maternal age, previous tubal surgery, and infertility, prior use of an intrauterine device (IUD), smoking, and history of genital infections were listed as potential risk factors for EP [17]. However, it is important to note that some patients may experience EP without having these established risk factors. Hence, our study sought to investigate if there are any predictive factors specifically for primigravid women without known risk factors. Our findings suggest that advanced age and lower BMI show potential for predicting ectopic pregnancy in this particular group.

The reasons behind the increased risk of EP in older women are not yet fully understood. Some theories propose age-related changes in tubal function, which might lead to delays in ovum transport and subsequent tubal implantation [18].

Furthermore, we observed that underweight women are also at higher risk for ectopic pregnancy according to our results. While limited studies have explored the relationship between EP and BMI, a retrospective study found that women with a BMI below 18.5 kg/m² face an increased risk of EP [19]. However, the exact mechanisms causing ectopic pregnancy in underweight women have not been thoroughly investigated.

It is well-established that underweight women are at risk of miscarriage and pregnancy complications, but the precise link between low BMI and ectopic pregnancy remains unresolved. Further research is needed to fully comprehend the mechanisms behind these associations and to better understand the relationship between low BMI and ectopic pregnancy in underweight women.

The retrospective design and small sample size limit the generalizability of our results. However, as far as we could find our study is the first which presents the EP risk factors for primigravid women. We identified advanced age and lower BMI as potential indicators. We conducted a ROC analysis to investigate the existence of a statistically significant threshold value that amplifies the risk of ectopic pregnancy concerning age and BMI. Our findings yielded a substantial area under the curve, enabling us to establish a threshold value. Notably, the scarcity of studies providing threshold values for ectopic pregnancy in the existing literature underscores the uniqueness of our study. Despite the modest

sample size and the inherent limitations in the clinical applicability of our results, we hold the view that our pilot study significantly enriches the literature. Our approach, which diverges from the existing research landscape, promises to enhance the understanding of ectopic pregnancy risk assessment.

Collectively, the findings from our study and literature highlight the complexity of understanding ectopic pregnancy risk factors. While some factors have been clearly identified, a substantial portion of cases remains unexplained, emphasizing the need for further research in this area. Improved risk prediction models that incorporate a combination of factors may lead to better early detection and more effective prevention strategies, ultimately reducing the burden of ectopic pregnancies on affected women and healthcare systems. Continued collaborative efforts between researchers and healthcare professionals are crucial to advance our knowledge and improve outcomes for women at risk of ectopic pregnancy.

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References

[1]Rana P, Kazmi I, Singh R, et al. Ectopic pregnancy: a review. Arch Gynecol Obstet. 2013;288(4):747-57.

[2]Lurie S. The history of the diagnosis and treatment of ectopic pregnancy: a medical adventure. Eur J Obstet Gynecol Reprod Biol. 1992;43(1):1-7.

[3] Alkatout I, Honemeyer U, Strauss A, et al. Clinical diagnosis and treatment of ectopic pregnancy. Obstet Gynecol Surv. 2013;68(8):571-81.

[4]Dart RG, Kaplan B, Varaklis K. Predictive value of history and physical examination in patients with suspected ectopic pregnancy. Ann Emerg Med. 1999;33(3):283-90.

[5]Dimitry ES, Atalla RK. Modern lines of management of ectopic pregnancy. Br J Clin Pract. 1996;50(7):376-80.

[6]Mullany K, Minneci M, Monjazeb R, et al. Overview of ectopic pregnancy diagnosis, management, and innovation. Womens Health (Lond). 2023;19:17455057231160349.

[7]Scibetta EW, Han CS. Ultrasound in Early Pregnancy: Viability, Unknown Locations, and Ectopic Pregnancies. Obstet Gynecol Clin North Am. 2019;46(4):783-795.

[8]Xiong X, Buekens P, Wollast E. IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies. Contraception. 1995;52(1):23-34.

[9]Leach RE, Ory SJ. Management of ectopic pregnancy. Am Fam Physician. 1990;41(4):1215-22.

[10] Senterman M, Jibodh R, Tulandi T. Histopathologic study of ampullary and isthmic tubal ectopic pregnancy. Am J Obstet Gynecol. 1988;159(4):939-41.

[11] den Heijer CDJ, Hoebe CJPA, Driessen JHM, et al. Chlamydia trachomatis and the Risk of Pelvic Inflammatory Disease, Ectopic Pregnancy, and Female Infertility: A Retrospective Cohort Study Among Primary Care Patients. Clin Infect Dis. 2019;69(9):1517-1525.

[12] Tuomivaara L, Rönnberg L. Ectopic pregnancy and infertility following treatment of infertile couples: a follow-up of 929 cases. Eur J Obstet Gynecol Reprod Biol. 1991;42(1):33-8.

[13] Dekeyser-Boccara J, Milliez J. Tabac et grossesse extra-utérine: y a-t-il un lien de causalité? [Smoking and ectopic pregnancy: is there a causal relationship?]. J Gynecol Obstet Biol Reprod (Paris). 2005;34 Spec No 1:3S119-23.

[14] Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. Clin Obstet Gynecol. 2012;55(2):376-86.

[15] Shaw JL, Dey SK, Critchley HO, et al. Current knowledge of the aetiology of human tubal ectopic pregnancy. Hum Reprod Update. 2010;16(4):432-44.

[16] Jenabi E, Ayubi E, Khazaei S, et al. The environmental risk factors associated with ectopic pregnancy: An umbrella review. J Gynecol Obstet Hum Reprod. 2023;52(2):102532.

[17] Bouyer J, Coste J, Shojaei T, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol. 2003;157(3):185-94.

[18] Yeko TR, Handler A. The effect of aging on tubal function and ectopic pregnancy. Semin Reprod Endocrinol 1991;9:215–20.

[19] Cai J, Liu L, Jiang X, et al. Low body mass index is associated with ectopic pregnancy following assisted reproductive techniques: a retrospective study. BJOG. 2021;128(3):540-550.