ORIGINAL RESEARCH

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Is Decreased Serum AMH Level an Independent Risk Factor for Ectopic Pregnancy?

Düşük Serum AMH Seviyesi Ektopik Gebelik için Bağımsız Bir Risk Faktörü müdür?

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Abstract

Objective: The aim of this study was to investigate the possible relationship between the frequency of tubal ectopic pregnancy and serum anti-Mullerian hormone (AMH) levels.

Method: In this prospective study, a comparison is made between a group of 106 healthy women and a group of 106 women who were diagnosed with first-trimester tubal ectopic pregnancies through natural conception. Although no known reason for ectopic pregnancy was identified, patients diagnosed with ectopic pregnancy and hospitalized were included. The ectopic pregnancy group comprised women aged 22-43 years, and the control group comprised women aged 22-40 years. Women known to have low ovarian reserve were excluded, as were women with a family history of premature ovarian failure, and those with additional causes that may decrease ovarian reserve, such as pelvic surgery. In addition, cervical, heterotopic, ovarian, or ectopic pregnancies of unknown location were excluded from the study. Serial beta-human chorionic gonadotropin and transvaginal ultrasonography were used for the diagnosis of ectopic pregnancy, along with the measurement of serum AMH level as an indicator of ovarian reserve.

Results: In both groups, a lower serum AMH level was negatively correlated with increasing age (r=-0.210, p<0.01), and the ectopic pregnancy group had lower serum AMH levels (1.51 and 3.69 ng/mL, respectively, p<0.001) than healthy women of equivalent age. Ectopic pregnancy was found to increase 1.7 times with each 1-ng/mL decrease in AMH.

Conclusion: According to the results of the study, decreased serum AMH levels in women of all ages increased the frequency of ectopic pregnancy.

Keywords: Anti-Müllerian hormone, ectopic pregnancy, ovarian reserve

Öz

Amaç: Bu çalışmanın amacı, tubal ektopik gebelik sıklığı ile anti-Müllerian hormon (AMH) düzeyleri arasındaki olası ilişkiyi araştırmaktır.

Yöntem: Bu prospektif çalışmada, 106 sağlıklı kadından oluşan bir grup ile spontan ilk trimester tubal ektopik gebelik tanısı konan 106 kadından oluşan bir grup arasında bir karşılaştırma yapılmıştır. Ektopik gebelik için bilinen bir neden olmamasına rağmen, ektopik gebelik tanısı konan ve hastanede yatarak tedavi edilen hastalar dahil edilmiştir. Ektopik gebelik grubu 22 ila 43 yaşları arasındaki kadınlardan, kontrol grubu ise 22 ila 40 yaşları arasındaki kadınlardan oluşmuştur. over rezervi olduğu bilinen kadınlar, ailesinde prematüre over yetmezliği öyküsü olan kadınlar ve pelvik cerrahi gibi over rezervini azaltabilecek ek nedenleri olan kadınlar çalışma dışı bırakılmıştır. Ayrıca, servikal, heterotopik, ovarian gebelikler ve yeri bilinmeyen ektopik gebelikler çalışma dışı bırakılmıştır. Ektopik gebelik tanısı için seri beta-insan koryonik gonadotropin ve transvajinal ultrasonografi, over rezervi testi olarak da serum AMH değeri kullanılmıştır.

Bulgular: Her iki grupta da artan yaşla negatif korelasyon gösteren daha düşük serum AMH değeri bulduk (r=-0,210, p<0,01). Ektopik gebelik grubunun, aynı yaştaki sağlıklı kadınlara kıyasla daha düşük serum AMH düzeyi (sırasıyla 1,51 ve 3,69 ng/mL, p<0,001) olduğunu bulduk. AMH düzeyindeki her 1 ng/mL'lik düşüş ile ektopik gebelik 1,7 kat arttı.

Sonuç: Araştırmamız sonuçlarına göre doğurganlık çağındaki kadınlarda azalmış serum AMH düzeyleri ektopik gebelik oranını artırmaktadır.

Anahtar kelimeler: Anti-Müllerian hormon, ektopik gebelik, over rezervi

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Introduction

An ectopic pregnancy is a blastocyst implantation outside the endometrium. The incidence of ectopic pregnancy among all pregnancies is 12% (1). The mortality rate of ectopic pregnancy is 0.48 per 100,000 live birth (2).

Known risk factors for ectopic pregnancy include smoking, intrauterine device use, previous ectopic pregnancy, pelvic infection and surgery, and tube diseases. In addition, ectopic pregnancies in artificial reproductive technology (ART) pregnancies are observed 2.55 times more frequently than normal pregnancies (3,4).

The ovary and the endocrine environment it creates after ovulation affect the journey of the blastocyst and its attachment to the endometrium. A healthy ovary is therefore essential for the formation and continuation of pregnancy. The relationship between decreased ovarian function and ectopic pregnancy is not clear. Regardless of the embryo transfer technique, ectopic pregnancy develops more frequently than spontaneous pregnancies in women with decreased ovarian reserve who undergo ART. In fact, decreased ovarian reserve during ART cycles is considered an independent ectopic pregnancy risk factor (5).

Half of the women diagnosed with ectopic pregnancy had no risk factors (6). Both this situation and the increase in ectopic pregnancies in ART pregnancies, independent of the embryo transfer technique, … a relationship between the decrease in ovarian reserve and ectopic pregnancy.

To the best of our knowledge, no study has yet investigated the relationship between ectopic pregnancy risk and ovarian reserve in natural pregnancies. In this study, we aimed to investigate whether the frequency of ectopic pregnancy is associated with ovarian reserve in spontaneously pregnant women who have not received assisted reproductive technology or infertility treatment.

Materials and Methods

According to the Declaration of Helsinki, this prospective study was performed with the permission of the Clinical Research Ethics Committee of a İstanbul Medipol University (dated: 23.06.21, decision no: 731).

The study was initiated after obtaining detailed verbal and written consent from all participants, with approval from the ethics committee. The study was conducted with a total of 212 women at a gynecology and obstetrics clinic at a tertiary health center from June 2021 to October 2022.

By October 2022, 150 hospitalized patients with ectopic pregnancy were included. Heterotopic pregnancies, women with autoimmune diseases, women with a history of pelvic infection, women with a history of pelvic surgery, women diagnosed with polycystic ovary syndrome, women with primary ovarian insufficiency (POI) or diminished ovarian reserve (DOR), women who smoked, women with previous ectopic pregnancies, and those with non-tubal ectopic pregnancy were excluded from the study. Ten patients who voluntarily left the hospital after hospitalization and six patients aged >45 years and 21 years were excluded. Two patients diagnosed with ectopic and heterotopic pregnancy were excluded from the study. After hospitalization, 13 patients with known risk factors for ectopic pregnancy (intrauterine device use less than two months ago, pelvic surgery, pelvic infection, systemic lupus erythematosus, patients with thyroid disease, women who smoke regularly, patients with previous ectopic pregnancy, etc.) and two patients with pregnancy that occurred while receiving infertility treatment were excluded from the study; related data were not processed, and the study was performed with the data of the remaining 106 patients.

In the control group, 106 healthy women who applied to the gynecology and obstetrics clinic for control or with a complaint of vaginitis were planned. Women with menstrual irregularities, endocrine diseases, early menopause in the family, obesity, anorexia, and who smoked were excluded from the control group. Ten of the 120 women were excluded from the study because they did not undergo blood testing, and four of them disclosed that they smoked later.

Finally, a total of 106 ectopic pregnancy patients (diagnosed with tubal ectopic pregnancy in the first trimester and conceived naturally) aged between 22 and 43 years and 106 healthy women aged between 22 and 40 years (routine check-ups or complaints of vaginitis) were included in the study. Age, pregnancy, and additional disease history of the patients were recorded. Transvaginal ultrasonography (GE Logic 200 Pro, 5 MHz vaginal probe) was performed in all patients. Blood was collected from each patient to measure the beta-human chorionic gonadotropin (BHcg) and anti-Mullerian hormone (AMH) values and then studied without waiting. Serum AMH levels were measured using the Elica technique (Roche E411, USA).

Although the BHcg value was the pregnancy level, women whose intrauterine gestational sac could not be seen or who had a gestational sac in the tube on ultrasonography were recorded as having an ectopic pregnancy. Since reliable data could not be obtained via ultrasonography in women with very low BHcg values, serial BHcg tests were performed

first, and women who did not show an acceptable increase were included in the study group.

A detailed anamnesis was obtained from the patients in the control group during their first examination. Then, during gynecological examination, ultrasonography was performed, and blood was drawn for AMH.

Statistical Analysis

Mean standard deviation and median interquartile range values are given in descriptive statistics for continuous data, and the number and percentage values are given in discrete data. The Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution.

An independent samples t-test was used to compare patient ages with and without ectopic pregnancy, and the Mann-Whitney U test was used to compare AMH values between the two groups.

Multivariate logistic regression analysis was used to determine whether age and AMH were effective risk factors for ectopic pregnancy.

The IBM SPSS version 20 (Chicago, IL, USA) software was used in the evaluations and $p<0.05$ was considered statistically significant.

In a study in which 106 patients with ectopic pregnancies and 106 patients were included as the control group, and the AMH values were compared as the primary outcome, the power of the test was found to be d=0.98 (effect size), Type I error =0.05, and power =0.99 (99%). The calculation was performed using GPower 3.1.9.2 software.

Results

The study included 106 women diagnosed with ectopic pregnancy and 106 healthy women. The minimum age of patients with ectopic pregnancy was 22 years, and the maximum age was 43. The mean age of both groups was 32 years, and no statistically significant difference was found ($p>0.05$). The minimum and maximum age of patients with ectopic pregnancy patients was 22 and the maximum age was 43 (Table 1).

All patients in the control group had been pregnant at least once previously, whereas 88 women (83%) in the ectopic pregnancy group had been pregnant previously.

One-third (30%) of the ectopic pregnancy group required surgical treatment.

The AMH level in the study group was between 0.04 and 7.35 ng/mL; in the control group was between 0.76 and 14.90 ng/mL.

A significant difference was found between the AMH values of the ectopic pregnancy group and the control group (respectively 1.51, 3.69 ng/mL, $p<0.001$). The AMH value was lower in the ectopic pregnancy group than in the non-pregnant group (Table 1).

In patients aged ≤24 years, 2530 years, 3135 years, 3640 years, AMH values were lower than the thresholds in the literature (3 ng/mL, 2.5 ng/mL, 1.5 ng/mL, 1 ng/mL, 1 ng/mL and 0.5 ng/mL, respectively) (50%, 61%, 50%, 46%, respectively) (Table 1). All three of the patients aged ≥40 years had AMH values below 0.5 ng/mL.

Six of the women with low AMH were aged 2030 years, 15 were aged 3040 years, and seven were aged 40 and over. A negative correlation was observed between patient age and AMH values ($r=-0.210$, $p<0.01$). The AMH values decreased as the patient age increased (Table 2).

As a result of the multivariate logistic regression analysis, the AMH values were found to be an effective factor for

Table 1. Comparison of age and AMH values of patients with ectopic pregnancy and control patients gravida, previous pregnancy, surgical therapy features of patients with ectopic pregnancy

	Ectopic pregnancy	Control	p-value
Age (years) mean ± SD	31.96±5.20	31.74±4.05	0.724[a]
AMH median (IQR)	1.51 (0.842.86)	3.69 (2.1014.90)	<0.001[b]
Gravida median (IQR)	3 (24)	2 (13)	0.05

[a]: Independent samples ttest, [b]: Mann-Whitney U test, SD: Standard deviation, AMH: Anti-Müllerian hormone, IQR: Interquartile range

Table 2. Correlation between the ages of every patient (n=212) and AMH

	Age	
	r	p
AMH	-0.210	0.002

AMH: Anti-Müllerian hormone

Table 3. Multivariate logistic regression analysis for age and AMH values considered to be effective on ectopic pregnancy

Variable	Regression coefficient (SE)	OR	95% CI		p-value
Age	-0.041 (0.035)	1.041	0.972	1.114	0.244
AMH	-0.548 (0.095)	1.730	1.434	2.083	<0.001

AMH: Anti-Müllerian hormone, OR: Odds ratio, CI: Confidence interval

ectopic pregnancy (p<0.001). Each 1-ng/mL decrease in AMH increased ectopic pregnancy by 1.730-fold (Table 3).

Discussion

In this study, we compared the ovarian reserves of healthy women and those diagnosed with ectopic pregnancy at similar ages. We found that the ovarian reserve decreased with increasing age. However, we found that ovarian reserve was lower in our ectopic pregnancy group regardless of age.

The incidence of ectopic pregnancy increases with increasing female age. While the incidence is 3% in women aged 20 years, it reaches 10% in women aged >40 years (7). This increase in the incidence of ectopic pregnancy can be explained by increasing age, decreased ovarian reserve, use of contraception methods, cumulative increase in infection, endometriosis, adhesion, surgery, and treatment for infertility. Accumulation of chromosomal abnormalities in the oocytes of women of advanced age, cumulus cell dysfunctions, and consequent deterioration of oocyte quality and acceleration in apoptosis are also associated with an increased risk of ectopic pregnancy (8). Therefore, decreased ovarian reserve may be one of the most important underlying factors in young women presenting with ectopic pregnancy. The patients in our study were mostly young women, only nine of whom (10%) were aged 40 years or older.

Studies have shown that decreased ovarian reserve is associated with ectopic pregnancy. In these studies, conducted with ART cycles, serum follicle-stimulating hormone/estradiol (FSH/E2) level was generally used as an ovarian reserve test. In this study, we used serum AMH levels rather than FSH/E2 or the antral follicle count as the ovarian reserve test. Although gonadotropin levels and antral follicle count are generally used as ovarian reserve tests, they may not be useful in diagnosing ectopic pregnancy as hormone levels are not reliable in terms of ovarian reserve due to physiological hypogonadism during pregnancy, and the number of antral follicles may also not be optimal for reasons such as pregnancy mass and intra-abdominal collection.

AMH is a marker reflecting the primordial cell pool. In our study, the AMH level also decreased as the age of the patient increases. There may be intra- and inter-assay variability in AMH tests, but there is no international standard monogram. However, considering its advantages, such as low intra- and intercycle variability and ease of use, and not being greatly affected by the use of oral contraceptives and gonadotropins, it can be said that it is sufficient to be used alone in the evaluation of ovarian reserve (9). AMH levels are lower in pregnancy than in the non-pregnant period. Moreover, as the gestational age increases, AMH decreases even more and increases again after delivery. In the literature, it has been reported that the mean AMH level in the first trimester is 1.69 ng/mL (if measured by ELISA) (10). All patients in our study group were in the first trimester (<13 weeks), and we detected AMH levels below 1.69 ng/mL in 58 of our patients. We accepted 1 ng/mL as the low cut-off value for ovarian reserve (11). In our study, 21 of the patients with low AMH were older than 40 years, and one-third of our patients (28 patients) in the ectopic pregnancy group had AMH <1 ng/mL. In accordance with the literature, we found that AMH decreased with increasing age. In addition to this natural decrease, we found low AMH levels in our ectopic pregnancy group, even in young patients. Furthermore, we observed that the risk of ectopic pregnancy increased 1.7-fold with each 1-unit decrease in AMH (Table 2).

It has been shown that the incidence of ectopic pregnancy in women undergoing ART is 13 times higher than the incidence of ectopic pregnancy in natural contraception pregnancies (2.03.5% vs. 1.52.0%) (12). This increased risk is attributable to both the woman's medical condition requiring ART (age, tubal diseases, endometriosis, etc.) and the direct ART technique. Although it was thought that an embryo with anomalies could not achieve the tubal journey due to an increase in the rate of chromosomal anomalies in women of advanced age who underwent ART, this could not be proven (13-15).

The incidence of ectopic pregnancy was found to be higher in women with DOR who underwent ART, with the increased rate attributed to poor oocyte quality, decreased

implantation capacity in the blast formed by fertilization of the oocyte, and implantation before reaching the cavity. However, considering that the possibility of ectopic pregnancy increases in advanced stages of ART cycles, … this will also be associated with decreased ovarian reserve.

The increase in the rate of ectopic pregnancy in young patients with low AMH levels supports this hypothesis, whereas studies with ovarian reserve mostly used FSH. Studies conducted with women with high FSH levels have also shown a relationship between low ovarian reserve and ectopic pregnancy [Lin et al (5)]. When ART was performed on women with FSH >10 IU/L, which is accepted as a low ovarian reserve criterion, ectopic pregnancies were observed more frequently. When confounding factors were eliminated, the authors concluded that only decreased ovarian reserve increased the rate of ectopic pregnancy in ART pregnancies and reported that decreased ovarian reserve is an independent risk factor for ectopic pregnancy (5).

In this study, which included patients with natural ectopic pregnancies, we also found a significant decrease in AMH among women diagnosed with ectopic pregnancy. The fact that we found that the risk of ectopic pregnancy increased approximately two-fold with every one unit of AMH decrease indicates that there is a direct relationship between ovarian reserve and the risk of ectopic pregnancy.

The decrease in ovarian reserve and increase in the incidence of ectopic pregnancy may be related to many factors. In women with DOR, a lack of hormone effects that ensure optimal endometrial receptivity development during embryo transfer is also a factor. DOR may be an independent risk factor for IVF/ET cycles, which is in line with the results of previous publications for patients considered to have reduced ovarian reserve based on FSH levels alone. This is likely due to deterioration of oocyte quality. This leads to decreased embryo quality, a suboptimal hormonal environment, and subsequent implantation failure. If endocrine factors are supported with medications, an increase in the possibility of intrauterine pregnancy may indicate the importance of hormonal changes (12,16). These factors may increase the risk of ectopic pregnancy. In immunohistochemical examinations, βcatenin was strongly expressed in tubal implantation sites in ectopic pregnancies following IVFET compared with non-pregnant tubal tissues. βcatenin, which is mainly localized at cellcell junctions, binds to Ecadherin and plays an important role in intercellular adhesion, cell polarity, and architecture (17-19). The downregulation of CXXC finger protein 5 (CXXC5) that increases βcatenin expression (19,20). CXXC5 is significantly downregulated in the corona radiata cells of women with DOR. This downregulation may lead to deterioration of the relationship between cumulus cells and oocytes and, therefore, to oocyte developmental disorders (21). Our patients were women with regulated menstruation who were not diagnosed with DOR or POI before ectopic pregnancy.

Study Limitations

One of the limitations of our study is that AMH levels were lower during pregnancy than in the non-pregnant period. However, while a general value of 1.69 ng/mL has been given in the literature for this value, we found a much lower limit value; therefore, we believe that our study is of some value.

Conclusion

We believe that advanced age is one of the most important factors in the increase in the incidence of ectopic pregnancy, for which there may be many reasons. We found that ovarian reserve was decreased in women who were ectopic. We believe that decreased ovarian reserve in women without risk factors may play a role in the etiology. This finding needs to be confirmed in a larger study.

Ethics

Ethics Committee Approval: According to the Declaration of Helsinki, this prospective study was performed with the permission of the Clinical Research Ethics Committee of a İstanbul Medipol University (dated: 23.06.21, decision no: 731).

Informed Consent: The study was initiated after obtaining detailed verbal and written consent from all participants, with approval from the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K.A., E.E.K., Concept: Ö.K.A., H.G., E.E.K., Design: Ö.K.A., H.G., E.O., D.E.A., Y.A.Ç., Data Collection or Processing: Ö.K.A., E.O., E.E.K., D.E.A., Y.A.Ç., Analysis or Interpretation: Ö.K.A., H.G., E.E.K., Literature Search: Ö.K.A., E.O., E.E.K., D.E.A., Y.A.Ç., Writing: Ö.K.A., H.G.

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