J Surg Med. 2020;4(1):25-28.
DOI: 10.28982/josam.670091

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Ovarian reserve testing in the prediction of recurrent pregnancy loss

Tekrarlayan gebelik kaybını öngörmede over rezerv testlerinin kullanılması

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Abstract

Aim: Approximately 1-2% of reproductive women have faced recurrent pregnancy loss (RPL). Ovarian reserve testing in the prediction of recurrent pregnancy loss is not usually performed. In this study, we aim to evaluate whether there were any differences between patients with and without a history of recurrent pregnancy loss (RPL) with regards to anti-Mullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (Lh), estradiol (E2) levels and basal follicle count.

Methods: This case-control study was conducted between 1 January 2013 and 1 January 2015 in the Gynecology and Obstetrics Clinic of Adana Numune Training and Research Hospital. A total of 370 patients aged 17-37 years with a diagnosis of RPL during that 2-year period were contacted by telephone. Further evaluation was made of 40 patients who met the study criteria and gave verbal consent. Patients were called to the Gynecology Polyclinic for assessment on the 3rd day of their menstrual cycle, and a control group was formed of 40 patients with similar demographic characteristics who were referred to the Gynecology Polyclinic and met the study criteria.

Results: The mean basal follicle count was determined as 9.4 (2.7) in the study group and 8.9 (2.5) in the control group (P=0.092). The mean AMH values in the RPL and control groups were 3.50 (1.92) ng/mL and 3.66 (2.14) ng/mL, respectively (P=0.718). The mean FSH values in the RPL and control groups were 6.77 (1.87) mIU/mL and 7.01 (1.90) mIU/mL, respectively (P=0.494). Mean LH values were measured as 5.6 (1.8) mIU/mL in the study group and 4.9 (1.7) mIU/mL in the control group. Mean E2 values were 87.7 (83.9) pg/mL and 48.4 (27.9) pg/mL in the study and control groups, respectively.

Conclusion: While no difference was found between the RPL and control groups in respect of AMH and FSH values in the ovarian reserve tests, the basal follicle count of the patients with recurrent pregnancy loss was found lower than that of the control group.

Keywords: Recurrent pregnancy loss, Ovarian reserve, AMH, Basal follicle count, FSH

Öz

Amaç: Üreme çağındaki kadınlarının yaklaşık %1-2'si tekrarlayan gebelik kaybı (RPL) ile karşı karşıyadır. Tekrarlayan gebelik kaybının öngörülmesinde yumurtalık rezerv testi genellikle yapılmaz. Bu çalışmamızda Antimüllerian hormon, follikül stimulant hormon, Lüteinizan hormon, Estradiol ve Bazal follikül sayısının tekrarlayan gebelik kabı olan ve olmayan hastalar arasında farklı olup olmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: 2 yıllık sürede tekrarlayan gebelik kaybı tanısı konulan, yaşları 17-37 yaş arası 370 hasta telefonla aranarak ayrıntılı sorgulama sonucu çalışma kriterlerine uyan ve sözlü onamları alınan 40 hasta tekrar değerlendirilmek üzere mensrüel siklusun 3. günü jinekoloji polikiniğe davet edildi. Çalışma grubu olarak alınan hastalarla aynı gün jinekoloji polikliniğine başvuran benzer demoğrafik özellikteki çalışma kriterlerine uyan 40 hasta kontrol grubu olarak oluşturuldu.

Bulgular: Tekrarlayan gebelik kaybı olan grupta ortalama bazal follikül sayısı 9,4 (2,7) adet, kontrol grubunda 8,9 (2,5) adet olarak ölçüldü. (P=0,092). Tekrarlayan gebelik kaybı olan grupta ortalama AMH değeri 3,50 (1.92) ng/mL, kontrol grubunda 3,66 (2,14) ng/mL, (P=0,718), FSH değeri tekrarlayan düşük yapan grupta 6,77 (1,87) mIU/mL, kontrol grubunda 7,01 (1,29) mIU/mL (P=0,494), LH değeri sırasıyla 5,6 (1,8) mIU/mL ve 4,9 (1,7) mIU/mL, E2 değeri sırasıyla 87,7 (83,9) pg/mL, 48,4 (27,9) pg/mL olarak ölçüldü.

Sonuç: Over rezevr testlerinden tekrarlayan gebelik kaybı olan grup ile kontrol grubu arasında AMH, FSH değerleri arasında fark bulunmazken, tekrarlayan gebelik kaybı olan grupta estradiol seviyesi daha yüksek, bazal follikül sayısı ise daha düşük bulundu.

Anahtar kelimeler: Tekrarlayan gebelik kaybı, Over rezervi, AMH, Bazal follikül sayısı, FSH

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Ethics Committee Approval: The study was approved by the Ethical Committee of Adana Numune Training and Research Hospital (2014/29).
Etik Kurul Onayı: Çalışma Adana Numune Eğitim ve Araştırma Hastanesi Etik Komitesi (2014/29) tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 1/20/2020
Yayın Tarihi: 20.01.2020

How to cite / Atıf için: Kükrer S, Arlıer S, Karaman SS. Ovarian reserve testing in the prediction of recurrent pregnancy loss. J Surg Med. 2020;4(1):25-28.

Introduction

The terminology of recurrent pregnancy loss (RPL) has still not been fully defined. To remove this confusion, in 2005, The European Society of Human Reproduction and Embryology (ESHRE) recommended that the definition of RPL be accepted as 3 or more consecutive pregnancies lost before the 22nd week [1]. Several factors have been held responsible in the etiopathogenesis.

The factors which are primarily thought to be responsible are maternal and paternal chromosomal anomalies (this risk is greater in cases of marital consanguinity), auto-antibodies, natural killer cell dysfunctions, abnormal HLA-G expression, hereditary or acquired thrombophilia, thyroid auto-antibodies, polycystic ovary disease (PCOD), sperm DNA fragmentation, impaired endometrial receptivity, uterine malformations and lifestyle-associated problems such as excessive alcohol consumption or obesity [2].

Anti-Mullerian hormone (AMH), glycoprotein in structure, prevents the development of paramesonephric canals (Mullerian canals) in a male embryo and is encoded by the AMH gene in the transforming growth factor (TGF-beta) family. In the female fetus, it initiates the proliferation of granulosa cells of the preantral and small antral follicles towards the end of fetal life and particularly postnatally [3].

As females age, AMH within the follicle decreases along with AMH serum concentrations. Aging cases a gradual deterioration in oocyte quality. A stronger correlation is shown of oocyte quality and basal follicle count compared to E2 and FSH in this drop in AMH levels [4].

The formation of maternal non-disjunctions during oogenesis and the emergence of chromosomal abnormalities in the embryo which have developed as a result of impairments in the spindles may cause embryo and fetus losses [5,6]. In parallel with a decreasing ovarian reserve, the increasing rate of aneuploidy in oocytes has been shown to cause miscarriages as well as reduced fertility [7-9].

The aim of this study was to reveal whether or not there was a relationship between falling AMH levels due to a diminishing ovarian reserve and recurrent pregnancy loss. It was thought that different results may emerge as few previous studies have been made with selection and randomization of the study groups, and control groups have included very high AMH values such as in PCOD.

Materials and methods

This prospective case-control study was conducted between 1 January 2013 and 1 January 2015 in the Gynecology and Obstetrics Clinic of Adana Numune Training and Research Hospital. Patients aged 17-37 years with a diagnosis of recurrent pregnancy loss during that 2-year period were included as the study group, and contacted by telephone and recalled to the Gynecology Outpatient clinic for assessment on the 3rd day of their menstrual cycles. Of the total 370 patients with RPL in the previous 2 years, 158 presented at the outpatient clinic. A detailed anamnesis was taken from each patient. The previous tests were recorded and family history was questioned. A detailed gynecological examination was performed with transvaginal ultrasonography using a 5-7 MHz vaginal probe (TV-USG Mindray, DC-7 Nanshan Shenzhen P.R. China).

On day 3 of the menstrual cycle, between 08:00 and 12:00, a fasting venous blood sample was withdrawn into a sterile tube containing no other material (Becton-Dickinson, Vacutainer, Z). After waiting for 30 minutes, serum was separated by centrifugation at 2000 rpm. Analysis was made with chemoluminescence immunoassay method for endocrine tests such as FSH, LH, PRL, T3, T4, TSH (thyroid auto-antibodies were requested from those with impaired thyroid tests) (Roche Cobas 6000 e601, Roche Diagnostics, Mannheim, Germany).

A blood sample was concurrently obtained from all patients for AMH measurement. Serum was separated by centrifugation at 2000 rpm then stored at -20° until analysis. The AMH concentration was measured with the ELIZA enzyme immunoassay method (Immunotech, Beckman Coulter, Marseilles, France). Antiphospholipid antibody, HgbA1c (glycolised hemoglobin), liver function tests, hemogram and spermiogram tests were performed.

Exclusion criteria from the study included patients who were pregnant, smoked cigarettes or drank alcohol, those with marital consanguinity, with abnormal karyotype analyses, abnormal findings on trans-vaginal ultrasonography (an appearance consistent with endometrioma, hydrosalpinx, etc), a previous diagnosis of endometriosis, with partners with abnormal spermiograms, connective tissue or immunological diseases, systemic diseases (diabetes mellitus, hypertension, PCOD – according to the Rotterdam criteria) or other endocrinological disorders, those without low values in 3 or more of the ESHRE criteria, those with an abnormal finding on hysterosalpingography (HSG), body mass index (BMI) >30, a history of gynecological surgery or if consent was not given for participation in the study.

The control group consisted of patients of similar age and demographic characteristics who attended the Gynecology outpatient and had no history of pregnancy loss, did not have PCOD and had a regular menstrual cycle. Fasting blood samples were drawn from both the patient and control groups in the morning of the 3rd day of the menstrual cycle.

Approval for the study was granted by the Ethics Committee of Adana Numune Training and Research Hospital. After detailed explanations, informed consent was obtained from all participants. In the control group, a record was made for each participant of age, menstrual status, number of pregnancy losses, smoking habits and alcohol habits. BMI was calculated from the height and weight values.

Forty patients and 40 control groups subjects who all met the study criteria were evaluated.

Statistical analysis

Statistical analysis was performed with Statistics Package for Social Sciences (SPSS) [SPSS 21 Inc., Chicago, IL, USA] software. Independent groups were compared with the Independent samples t-test. For non-parametric data, the Mann Whitney U-test and the Chi-square test were used. A value of $P < 0.05$ was considered statistically significant.

Results

The study included 40 patients with recurrent pregnancy loss (RPL) and a control group of 40 healthy volunteers. The mean age was 30.2 (4.5) years in the study group and 28.3 (5.7) years in the control group. The mean BMI value was calculated as 22.6 (1.9) in the study group and 21.7(1.7) in the control group. The number of pregnancy losses was recorded as 3 in 27 patients, 4 in 9 patients, 5 in 3 patients and 6 in 1 patient. None of the study or control group subjects smoked cigarettes or consumed alcohol. The demographic characteristics and the laboratory findings of both groups are shown in Table 1.

The mean basal follicle count was measured as 9.4 (2.7) in the study group and 8.9 (2.5) in the control group, which were similar (P=0.092).

The mean AMH value was determined as 3.50 (1.92) ng/mL in the study group and 3.66 (2.1) ng/mL in the control group (P=0.718). The mean FSH value was determined as 6.77 (1.87) mIU/mL in the study group and 7.01 (1.29) mIU/mL in the control group (P=0.494). The distribution of the basal follicle count and AMH values is shown in Figure 1.

Table 1: Distribution of the demographic and laboratory values of both groups

	Control group n=40	Study group n=40	Total	*P*-value
Age (years)	28.3 (5.7)	30.2 (1.9)	29.3 (5.2)	0.149
AMH Level (ng/mL)	3.66 (2.1)	3.50 (1.9)	3.6 (2.0)	0.718
FSH Level (mIU/mL)	7.0 (1.3)	6.7 (1.8)	6.9 (1.6)	0.494
LH Level (mIU/mL)	4.5 (1.7)	5.6 (1.8)	5.3 (1.8)	0.607
E2 Level (pg/mL)	48.4 (27.9)	87.7 (89.9)	68.0 (65.2)	<0.001
Basal follicle count	9.4 (2.8)	8.9 (2.5)	9.2 (2.6)	0.092
BMI	21.7 (1.7)	22.6 (1.9)	22.2 (1.8)	0.227

Data as presented mean (SD), SD: Standard deviation, BMI: Body mass index

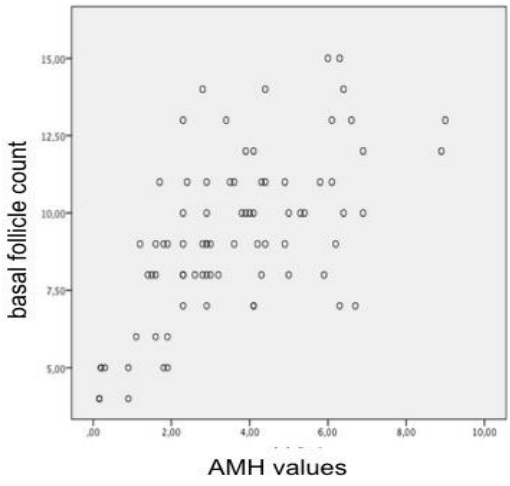

Figure 1: Distribution of basal follicle count and AMH values

Discussion

Reduced rates of becoming pregnant, together with increased rates of the birth of infants with anomalies and rates of miscarriage are seen with increasing age and decreasing ovarian reserve [10,11]. The probable reason for this is thought to be the diminished quality of the eggs remaining in the reduced ovarian reserve associated with increasing age [12]. The extended exposure of eggs to toxic mutant agents due to increased maternal age may be the cause of a deterioration in quality due to DNA damage and the formation of DNA methylation [13].

Basal follicle count and 3rd day FSH values have been used for many years in the determination of ovarian reserve. AMH measurement, which is strongly correlated with antral follicle count, has started to be used routinely in many clinics at the start of IVF treatment besides the determination of ovarian reserve, especially in patients with PCOD and before endometrioma surgery [14]. As AMH measurement can be made on any day of the cycle, it has the advantage of facilitating analysis in patients where the ovarian reserve is evaluated. Previous studies related to AMH have generally been conducted on infertile patient groups [4].

Most studies of patients with a diagnosis of endometriosis have included a pre and post- surgical evaluation of ovarian reserve. In studies by Chang et al, the relationship between laparoscopic cystectomy and ovarian reserve was investigated with 3D-USG evaluation of the ovarian volume and AMH levels. A decrease in serum AMH levels on the 7th postoperative day was determined in both groups of patients with ovarian cysts and no endometrioma. At the 3rd postoperative month, this fall in the AMH levels had increased to 65% of the preoperative level. However, in that study, no detailed information was available with respect to the history of pregnancy loss [15].

The vast majority of these cases of RPL may be due to reasons such as defective chromosomes carried by the mother or father, genetic damage occurring in the formation of the embryo, maternal metabolic or endocrine diseases, maternal hereditary or acquired thrombophilic diseases, functional or structural defects in the uterus or endometrium or maternal immune disorders. Despite a comprehensive investigation of patients, the etiology of recurrent miscarriage is not identified in 50% of cases [16].

Furthermore, it has recently been shown that apoptosis mechanisms play a significant role in placental development and differentiation and tissue homeostasis. The interaction of Fas ligand (fasL) with decidual cells in the uterine wall internal layer was seen to provide down-regulation on the active leukocytes in that area. This adjusts the levels of cytokines such as TGF-beta and IL-10 and provides trophoblastic invasion in an appropriate form. Leukocyte infiltration into the implantation area occurs when this substance is absent or decreased in decidual cells [17].

It has been suggested in previous research that the inhibition of trophoblastic invasion with this mechanism could be a possible reason for recurrent pregnancy loss. Some studies have also implied that the decrease in bcl-2 expression and increase in bax expression in decidual cells could be the reason for RPL [18]. Studies on the subject will shed light on the molecular mechanism and treatment choices in RPL.

In patients with high AMH levels, a greater number of follicles can be obtained with gonadotropin stimulation in IVF treatment. The rate of success with live births can be predicted when the AMH cut-off level is taken as 7.5pmol/L (1.05ng/mL). A relationship has been shown between AMH and oocyte quality which is not affected by the age of the woman. This relationship has been shown to be particularly stronger with follicular fluid AMH level rather than serum AMH level [19].

Prior studies have suggested that low anti-Mullerian hormone level (≤0.4ng/mL) is associated with an increased risk of miscarriage [20]. In the current study, a statistically significant relationship was determined between AMH and the antral follicle count. Similarly, in another study, a statistically significant correlation was found between the AMH level and antral follicle count [21]. Studies have been conducted on the correlation of premature ovary ageing and RPL, the reduction shown in oocyte

number and quality with this ageing of the ovaries and the level of serum FSH as an indirect indicator of this disorder [22]. In a study where young oocytes were donated to patients over 40 years of age who were undergoing IVF treatment, the rate of pregnancy loss was determined as 11.1% in the follow-up of those who became pregnant. This finding suggests that maternal and paternal factors together could play a role in spontaneous abortion [23]. Despite the reporting of various data regarding Y-chromosome micro-deletions, sperm DNA fragmentation due to oxidative stress, sperm morphological impairments, reduced concentration and impaired sperm motility which could cause RPL, no clear findings have emerged of the role of sperm in unexplained RPL [24]. In the current study, as it was considered that impaired sperm parameters could be associated with the result, RPL patients with impaired spermiogram parameters were excluded from the study.

Previous results reveal that maternal diminished ovarian reserve and low AMH level is related with increased risk of embryo aneuploidy in women of advanced age [25]. On the contrary, recent studies concluded that maternal serum AMH levels may not be a marker for fetal aneuploidy and healthy fetuses [26].

In another study of the relationship of AMH level and pregnancy loss, one hundred fifty-five RPL patients were examined. In a univariate logistic regression, AMH value <1 ng/mL was found related to diminished likelihood of live birth (OR 0.38; CI 0.16-0.87, P=0.03) [27]. Although the AMH level of the RPL group was slightly lower, it was not statistically significant.

In our present study, estradiol levels were found to be statistically significant between the study and control groups. We believe that this difference should be investigated in large patient populations whether the difference is incidental or not from the study group.

Several studies have researched the correlation between AMH and other markers of ovarian reserve. The correlation of AMH and different sizes of antral follicle has been previously investigated and the strongest correlation was found to be between AMH and antral follicles >5-6 mm in size, with the correlation coefficient reported to be as low as 0.41. The lack of an international assay standard for AMH measurements may explain these different results [28].

Limitations

One of the limitations of the study was the relatively small number of patients and the fact that it was single-centered.

Conclusion

While a significant correlation was determined between RPL and antral follicle count, the fact that no significant correlation was determined between high serum FSH level and low serum AMH level suggests that several complex agents other than diminished ovarian reserve could play a role in recurrent pregnancy loss. There is a need for further studies including molecular and genetic examinations to clarify the etiopathogenesis.

Acknowledgments

The authors thank Ümit Ali Kayışlı for his contribution to this research.

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The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine