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Is there a relationship between the psychological state of infertile patient and ovarian reserve indicators?

İnfertilite hastalarının psikolojik durumu ile over rezervi göstergeleri arasında bir bağlantı var mı?

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Abstract

Objective: This study explored the relationship between reduced ovarian reserve and the psychological state of infertile women.

Materials and Methods: This cross-sectional, single-center study was conducted with 106 infertile women. The Beck Depression Inventory (BDI) was used to assess patients' propensity for depression. The data relating to infertility, such as causes of infertility, type of infertility (primary or secondary), duration of infertility, and treatment status [previous assisted reproductive technologies (ART) treatment and ART treatment failure] were recorded for each patient. The ovarian reserve was determined using laboratory tests [anti-Mullerian hormone (AMH); follicle-stimulating hormone (FSH)] and transvaginal ultrasonography to measure the antral follicle count (AFC) in each ovary.

Results: There was no significant relationship between the total score obtained from the Beck depression scale and AFC, AMH, thyroid-stimulating hormone, FSH, estradiol, and prolactin measurements (p>0.05). There was no significant difference between the groups regarding depression levels based on the cause of infertility (p=0.412). Additionally, the type of infertility (primary, secondary) did not differ between the groups (p=0.586). There were no differences on the BDI scale regarding the level of depression between patients who underwent in vitro fertilization (IVF) treatment (history of previous IVF treatment failure) and those who did not.

Conclusion: There was no significant association between AFC and AMH levels and the depression state of infertile patients.

Keywords: Infertility, ovarian reserve, mood disorders, depression

Öz

Amaç: Bu çalışmanın amacı, azalmış over rezervi ile infertil hastaların depresyon eğilimi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Bu kesitsel tek merkezli çalışma 106 infertil kadın ile yürütülmüştür. Hastaların depresyon eğilimini değerlendirmek için Beck Depresyon Envanteri (BDE) kullanıldı. İnfertilite ile ilgili veriler: İnfertilite nedenleri, infertilite tipi (primer ve sekonder), infertilite süresi, tedavi durumu [önceki yardımcı üreme teknolojileri (YÜT) tedavisi ve YÜT tedavi başarısızlığı] her hasta için kaydedildi. Over rezervi laboratuvar testleri [anti-Mullerian hormonu (AMH); folikül uyarıcı hormon (FSH)] ve her bir overdeki antral folikül sayısını (AFC) ölçmek için transvajinal ultrasonografi kullanılarak belirlendi.

Bulgular: BDE'den elde edilen toplam puan ile AFC, AMH, tiroid uyarıcı hormon, FSH, estradiol ve prolaktin ölçümleri arasında anlamlı bir ilişki yoktu (p>0,05). İnfertilite nedenine göre depresyon düzeyleri açısından gruplar arasında anlamlı bir fark bulunmamıştır (p=0,412). Ek olarak infertilite tipine (primer, sekonder) göre gruplar arasında farklılık yoktu (p=0,586). YÜT tedavisi gören (daha önce YÜT tedavisi başarısızlığı öyküsü olan) ve görmeyen hastalar arasında depresyon düzeyi için BDE ölçeğinde fark yoktur.

Sonuç: AFC and AMH düzeyleri ile infertil hastaların depresyon durumu arasında anlamlı bir ilişki saptanmadı.

Anahtar Kelimeler: İnfertilite, over rezervi, duygudurum bozuklukları, depresyon

PRECIS: We evaluated the relationship between reduced ovarian reserve and the psychological state of infertile patients.

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Introduction

Infertility is defined as the inability of a couple to conceive after 12 months of regular unprotected intercourse[1]. Worldwide, infertility is estimated to affect 8-12% of couples of reproductive age[2]. The importance of poor ovarian responders was reemphasized by Drakopoulos et al.[3] in 2020; in their study, the authors rated this condition as frustrating for both the patient and fertility expert. Low ovarian reserve is a cause of infertility, which is clinically associated with a poor response to gonadotropin stimulation and a low success rate of in vitro fertilization (IVF) cycles[4]. Several factors are associated with poor ovarian response. The Bologna Criteria for poor ovarian response has recently been defined as follows: patient age (⩾40 years), previous poor ovarian response experience with ⩽3 oocytes retrieved after conventional stimulation and/or an abnormal ovarian reserve test, antral follicle count (AFC) <7 or anti-Mullerian hormone (AMH) <1.1 ng/mL)[5].

Currently, AMH, follicle-stimulating hormone (FSH), and AFC are markers used to determine ovarian reserve. Unlike FSH, the most important feature of AMH is that it is a marker that can be used regardless of the menstrual cycle. This feature facilitates the use of AMH as a laboratory parameter for ovarian reserve determination on the day of the patient's admission. Therefore, the use of AMH for patients with infertility has increased in recent years in gynecological practice[6]. Another useful tool for investigating ovarian reserve is transvaginal ultrasonography (TVUS), which provides an instant (momentary) overview of AFC. Using TVUS, we can measure the number of primordial follicles in each ovary.

The association between hormonal dysfunction and mood-related disorders is a topic "under the magnifying glass" for many scientists worldwide[7]. Thyroid dysfunction is the most common autoimmune endocrine disease in women of reproductive age and is associated with menstrual irregularities, anovulation, and infertility. Hypothyroidism is considered a potential risk factor for female infertility. Atis et al.[8] showed that a significant percentage of women with clinical and subclinical hypothyroidism have sexual dysfunction. Impairment of sexual function is an important indicator of depression and related pathologies[9]. The study by Atis et al.[8] showed that hyperprolactinemia, hyperlipidemia, and depression were associated with female sexual dysfunction in clinical hypothyroidism. In another study, the authors explained an increased risk of depression in women compared with men because of fluctuations in estrogen levels that occur during reproductive cycle events, especially during the menopausal transition[10]. There are studies in the literature showing the relationship between depressive disorders and the premature ovarian aging process[11,12]. In the present study, we aimed to explore the relationship between poor ovarian reserve (POR) and the psychological state (tendency to depression) of infertile women.

Materials and Methods

This cross-sectional study, with 106 infertile women, was conducted in our public academic tertiary hospital between 08/15/2021 and 01/15/2022. All patients were divided into four groups according to the cause of infertility (female, male, both genders, and unexplained infertility). All participants were informed about the subjects of this study. The study inclusion criteria were volunteering to participate, being examined for infertility in our hospital, and patient data accessibility. Study exclusion criteria were patients who did not agree to participate in the investigation, those who applied to our hospital for infertility but did not undergo a detailed laboratory and ultrasonographic examination, and conditions or diseases that prevented filling questionnaires, such as loss of vision, hearing or sensory, motor, and cognitive (dementia, psychosis) skills.

Demographic and social characteristics (age, education level, employment status, financial status) and obstetric characteristics (number of gravidas, parities, history of abortion, and comorbid diseases) were evaluated in each group. The data relating to infertility, such as the causes of infertility (female, male, both, and unexplained infertility), type of infertility (primary or secondary), duration of infertility, duration of marriage (duration of the relationship with a partner), and treatment status [previous assisted reproductive technologies (ART) treatment, and ART treatment failure] were recorded for each patient. The ovarian reserve was determined using laboratory tests (AMH; FSH) and TVUS. We used TVUS to measure the number of antral follicles in each ovary[13]. Each patient underwent ultrasonography evaluation by two gynecologists, and AFC was determined for each ovary[14].

AFC was performed in the early follicular phase of the menstrual cycle; according to the assessment, we divided patients into three groups: normal ovarian reserve, POR, and patients with polycystic ovary morphology[15,16]. The study involved infertility patients whose levels of FSH, thyroid-stimulating hormone (TSH), estradiol (E2), and prolactin (PRL) were measured on the third day of the menstrual cycle. In addition, serum progesterone levels were measured in the midluteal phase of the menstrual cycle.

In our study, the Beck Depression Inventory (BDI) was used to identify the severity of depression[17]. We considered the BDI inventory "an indicator of the presence and degree of depressive symptoms" because of its worldwide use. BDI provides a psychiatric assessment of the depth of depression (severity of depressive symptoms). Inventory is a self-report questionnaire consisting of 21 questions (items). The answers were summed up to obtain a total score that ranged from 0 to 63, with the total score reflecting the severity of depression. There were four levels of depression according to the BDI scale:

- GROUP 1 (0-12): Minimal depression
- GROUP 2 (13-18): Mild depression
- GROUP 3 (19-29): Moderate depression
- GROUP 4 (30-63): Severe depression

After completing the questionnaire, the patient was referred to a psychiatrist for further evaluation, counseling, and treatment arrangements.

The study was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa City Hospital (approval number: 2021-13/9, date: 14.07.2021).

Statistical Analysis

The Shapiro-Wilk test was used to decide whether or not a sample fit a normal distribution. Continuous variables were expressed as median (minimum: maximum) values, whereas categorical variables were expressed as n (%) values. The Kruskal-Wallis test was used if normality was not observed. Categorical variables were compared using the chi-square test and Fisher-Freeman Halton test. The relationships between AMH, TSH, FSH, E2, and prolactin parameters and the total score obtained from the depression scale were analyzed using correlation analysis, and the Spearman correlation coefficient was calculated. To calculate the sample size needed in our study, the article published by Nicoloro-SantaBarbara et al.[18] was used as a reference study, and a priori power analysis was performed. The authors examined the magnitude and predictors of emotional responses to the diagnosis of infertility in two groups of women: those with diminished ovarian reserve (DOR) and those clinically diagnosed with an anatomical cause of infertility. In their study, the authors reported the infertility distress level as 137.05±32.21 for the DOR group (n=51) and 118.05±31.90 for the ACI group (n=51), and the effect size value calculated using these values was determined as d=0.59. As a result of the a priori power analysis, using the relevant effect size value (d=0.59), considering the type I error as 5% and the targeted power level as 80%, a total of n=106 subjects were included in the study, taking into account possible losses. Analyses were conducted using G*Power[19] and SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) program, and the significance level was set at α=5%.

Results

In total, 106 infertile women were included in the study. The median age of the participants in the study was 31 years. The median number for gravida and parity was 0. When the distribution was examined according to abortion status, the proportion of participants who had experienced abortion was 31.10%, whereas the proportion of participants who had not was 68.90%. The percentage of participants with chronic disease was 10.40%. The median marriage duration of the participants was 4 years, and the median infertility duration was 2 years. The proportion of participants with primary infertility was 65.10%, whereas that of those with secondary infertility-was 34.90%. When patients were examined according to the cause of infertility, it was found that 13.50% were due to male factors, 53.80% were due to female factors, 2.90% were due to both male and female factors, and 29.80% were due to unexplained infertility. It was determined that 56.60% of the participants had never received any treatment before, whereas 21.70% had previous treatment experience. The remaining 20.7% of the patients did not provide clear information about their previous treatment history. The median AMH (ng/mL) level of the patients was 2.87, whereas the median TSH (mIU/L) level was 2.28 (Table 1).

According to the BDI scale, no patients were found to be in group 4 with a score of more than 30, indicating severe depression. There was no significant difference between the groups regarding the depression state based on the cause of infertility (p=0.412). It was determined that there was no difference in marriage duration between the groups (p=0.264). Infertility duration also did not differ between the groups (p=0.169). The type of infertility did not differ between the groups (p=0.586). The treatment status did not differ between the groups (p=0.847), as was the case with the education level (p=0.645) and employment status (p=0.848). The financial status also

Table 1. General characteristics of participants in the study

Age, years (n=106)	31 (19:44)
Gravida (n=106)	0 (0:6)
Parity (n=106)	0 (0:3)
Abortion (n=106)	
Yes	33 (31.10%)
No	73 (68.90%)
Comorbid disease (n=106)	
Yes	11 (10.40%)
No	95 (89.60%)
Duration of marriage (n=106)	4 (0.33:21)
Duration of infertility (n=106)	2 (0.33:15)
Type of infertility (n=106)	
Primary	69 (65.10%)
Secondary	37 (34.90%)
Cause of infertility (n=104)	
Male	14 (13.50%)
Female	56 (53.80%)
Both	3 (2.90%)
Unexplained	31 (29.80%)
Treatment history (n=83)	
Absent	60 (56.60%)
Present	23 (21.70%)
AMH (ng/mL) (n=95)	2.87 (0.03:6.98)
TSH (mIU/L) (n=95)	2.28 (0.01:30.20)

Data were presented as median (minimum: maximum) and n%, AMH: Anti-Mullerian hormone, TSH: Thyroid-stimulating hormone

did not differ between the groups (p=0.487). There was no significant difference in AMH measurement (p=0.713), TSH measurement (p=0.520), or prolactin measurement (p=0.082) between the groups. Depression status did not differ between the groups based on the distribution of the right ovarian AFC (p=0.706) or left ovarian AFC (p=0.642) (Table 2).

There was no significant relationship between the total score from the depression scale and AMH, TSH, FSH, E2, and prolactin measurements (p>0.05) (Table 3).

Tablo 2. Comparisons of demographic and clinic characteristics according to depression status

	n	Group 1	n	Group 2	n	Group 3	p-value
Cause of infertility							
Male	55	7 (12.70%)	37	6 (16.20%)	12	1 (8.30%)	0.412[a]
Female		29 (52.70%)		17 (45.90%)		10 (83.30%)	
Both		1 (1.80%)		2 (5.40%)		0	
Unexplained		18 (32.70%)		12 (32.40%)		1 (8.30%)	
Duration of marriage	57	4 (0.33:21)	37	4 (0.50:17)	12	7 (1.17:20)	0.264[b]
Duration of infertility	57	2 (0.33:8)	37	1.50 (0.50:15)	12	2.50 (1:11)	0.169[b]
Type of infertility							
Primary	57	38 (66.70%)	37	22 (59.50%)	12	9 (75%)	0.586[c]
Secondary		19 (33.30%)		15 (40.50%)		3 (25%)	
Treatment history							
Absent	43	31 (72.10%)	34	24 (70.60%)	6	5 (83.30%)	0.847[a]
Present		12 (27.90%)		10 (29.40%)		1 (16.70%)	
Education level							
Below high school	57	14 (24.60%)	37	8 (21.60%)	12	5 (41.30%)	0.645[a]
High school		14 (24.60%)		8 (21.60%)		3 (25%)	
Above high school		29 (50.90%)		21 (56.80%)		54 (50.90%)	
Working status							
Employed	54	30 (55.60%)	36	18 (50%)	12	6 (50%)	0.848[c]
Unemployed		24 (44.40%)		18 (50%)		6 (50%)	
Financial status							
Below minimum wage	57	0	37	1 (2.70%)	12	0	0.487[a]
Minimum wage		20 (35.10%)		11 (29.70%)		4 (33.30%)	
Above minimum wage but less than 2 times		23 (40.40%)		14 (37.80%)		3 (25%)	
More than 2 times minimum wage		14 (24.60%)		11(29.70%)		5 (41.70%)	
AMH (ng/mL)	56	2.45 (0.03:9.11)	34	2.92 (0.02:6.40)	12	2.24 (0.03:5.90)	0.713[b]
TSH (mIU/L)	52	2.45 (0.01:30.20)	34	2.06 (0.34:6.41)	11	2.58 (0.01:7.90)	0.520[b]
Prolactin (µg/L)	51	21.60 (4.94:60.8)	28	18.90 (6.75:138)	12	12.15 (3.71:31.10)	0.082[b]
Right ovary							
POR	54	18 (33.30%)	34	14 (41.20%)	11	2 (18.20%)	0.706[a]
NOR		16 (29.60%)		10 (29.40%)		4 (36.40%)	
PCOM		20 (37%)		10 (29.40%)		5 (45.50%)	

Tablo 2. Continued

	n	Group 1	n	Group 2	n	Group 3	p-value
Left ovary							
POR	56	21 (37.50%)	36	14 (38.90%)	11	3 (27.30%)	0.642[a]
NOR		11 (19.60%)		11 (30.60%)		3 (27.30%)	
PCOM		24 (42.90%)		11 (30.60%)		5 (45.50%)	

POR: Poor ovarian reserve, NOR: Normal ovarian reserve, PCOM: Polycystic ovary morphology, The data are expressed as median (minimum: maximum) and n (%), [a]: Fisher Freeman Halton test, [b]: Kruskal Wallis test, [c]: Chi-square test, AMH: Anti-Mullerian hormone, TSH: Thyroid-stimulating hormone

Table 3. The relation between hormone levels and BDI score

n=106	BDI total score	
	r_s	p-value
AMH (ng/mL)	-0.44	0.662
TSH (mIU/L)	-0.04	0.650
FSH (mIU/L)	-0.02	0.807
E2 (ng/L)	-0.05	0.624
Prolactin (µg/L)	-0.14	0.170

r_s: Spearman correlation coefficient, AMH: Anti-Mullerian hormone, TSH: Thyroid-stimulating hormone, BDI: Beck Depression Inventory, FSH: Follicle-stimulating hormone, E2: Estradiol

Discussion

Infertility is a widespread concern that affects numerous couples globally. According to the World Health Organization, infertility is a "disease" of the reproductive system. It can be described as a "reproductive deficiency" that is not life-threatening and does not have physical impacts. However, reproductive deficiency may have detrimental effects on personality development, leading to frustration and weakening personality because most couples believe that having children is a life goal[20].

Infertility's consequences vary, including social impact, emotional breakdown, and severe distress in women's health. Birenbaum-Carmeli and Dirnfeld[21] highlight the importance of understanding the cultural and social context in which infertility occurs and is treated. However, the duration of the infertile period may play a key role in the psychological state of the infertile woman. Our study did not find a significant relationship between the duration of infertility and depression tendency (Table 2). We believe this is due to the short mean period of infertility in the patients in our study.

In some cultures, infertility is seen as a motherhood disability, which puts significant pressure on women to conceive and bear children[22]. This can lead to severe emotional distress, anxiety, and depression, especially if medical treatments are unsuccessful. This is why depression and other associated mood disorders can be seen in infertile women. Interestingly, the results of the present study did not show differences between primary and secondary infertility on the BDI scale in terms of the level of depression.

Hammarberg et al.[23] pointed out that while most women were satisfied with the treatment, many reported feeling anxious and stressed during the treatment process. Some women also reported experiencing depression and emotional difficulties, particularly if treatment was unsuccessful. Medicalization of infertility has inadvertently reduced the negative emotional reactions experienced by infertile couples[24]. Furthermore, advances in ART, such as IVF, offer hope to infertile couples who fear not becoming parents[25]. Perhaps this is how we can explain the lack of differences on the BDI scale for the level of depression between patients who underwent IVF treatment (history of previous IVF treatment failure) and those who did not in the present study. However, it is essential to acknowledge that infertility is a complex and emotionally charged issue that can significantly impact the mental health of individuals and couples. Atis et al.[8] found that hypothyroidism was associated with higher depression scores. In contrast, our study found no significant relationship between TSH levels and the BDI score. Atis et al.[8] also noted that mean PRL levels were significantly higher in patients with clinical and subclinical hypothyroidism. Our study found no difference in BDI scores based on hormone levels (Table 3).

One potential factor contributing to depression and other mood disorders in infertile women is ovarian dysfunction and POR. We know that a strong relationship exists between POR and treatment success. Infertile patients can have an idea about the success of the treatment because of doing individual research and being informed by the physician about the results of the tests. Considering all these conditions, a poor response to treatment with a POR may affect the psychological state of the patient compared with patients with normal ovarian reserve. Maki noted that women in the menopausal period commonly experience increased depressive symptoms and depressive disorders[26]. Frey et al.[27] also indicated that identifying individuals who might be at a higher risk for depression during the menopausal transition could guide preventive strategies for this population. The underlying mechanism for these symptoms is not fully understood, but it may involve the regulation of serotonin and norepinephrine by ovarian hormones. The authors also noted that this association requires

further research. Our study investigated the impact of impaired ovarian reserve on patients' psychological status. Following this goal, we examined the ovarian reserve of each patient using ultrasound and laboratory methods. Nicoloro-SantaBarbara et al.[18] reported that women with DOR had significantly higher infertility distress scores than women with anatomical causes of infertility. However, our study results did not show the impact of AFC and AMH values on the level (severity) of depression. This may be because this study's median duration of infertility was short (2 years), and the patients were well-informed about treatment regimens and treatment opportunities at our tertiary care center. Low ovarian reserve causes concern and may subsequently delay treatment and further evaluation of infertile patients[28]. However, the results of this study showed that there is no relationship between depression and low ovarian reserve. This is possible because of the development of ART worldwide and the easy availability of treatment methods in our country, which gives patients hope of conceiving.

Study Limitations

Our study has several limitations that should be considered when interpreting the results. First, the study's cross-sectional design does not allow us to conclude causality. Second, we only used self-report measures to assess depression and anxiety, which may not provide an accurate assessment of these conditions. Third, we assessed only the psychological state of women and did not consider the psychological state of their partners. Future research in this field should include a study with a control group.

Conclusion

Infertility is a complex issue with significant emotional and psychological consequences for both individuals and couples. Although medical procedures such as IVF can offer hope to infertile couples, they still experience stress and emotional instability during treatment. It is important to understand the cultural and social context in which infertility occurs and is treated and the potential factors that can cause depression and other mood disorders in infertile women. A factor facilitating the treatment process of women with infertility, and compliance with treatment, is the patient's psychological state. We examined the effect of ovarian reserve indicators on the psychological status of women with infertility. Our study results show that the impacted ovarian reserve is not a determinant of psychological status in infertile women.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa City Hospital (approval number: 2021-13/9, date: 14.07.2021).

Informed Consent: Informed consent was obtained from all participants included in the study.

Authorship Contributions

Concept: S.R.O., E.Ü., Design: S.R.O., Data Collection or Processing: S.R.O., Z.A., E.O, M.A.T., Analysis or Interpretation: B.B.Y., Literature Search: S.R.O., Z.A., Writing: S.R.O., Z.A., B.A.

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