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Comparison of Vitamin 25(OH)D and Anti-Müllerian Hormone Status in Infertile Patients with Polycystic Ovary Syndrome and with Diminished Ovarian Reserve

Polikistik Over Sendromlu ve Düşük Over Rezervli İnfertil Hastalarda 25(OH)D Vitamini ve Anti-Müllerian Hormon Seviyelerinin Karşılaştırılması

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Abstract

Objective: This study aimed to investigate the relationship between anti-Müllerian hormone and vitamin 25(OH)D levels in infertile patients with low ovarian reserve and polycystic ovary syndrome (PCOS).

Methods: The data of 153 infertile patients who applied to the infertility outpatient clinic were evaluated. Patients who met the PCOS criteria according to the Androgen Excess Society guidelines (group 1-PCOS) and patients with diminished ovarian reserve (DOR) (group 2-DOR) who had serum anti-Müllerian hormone levels <1 ng/mL were compared.

Results: When comparing patients with PCOS (n=78) and DOR (n=75), a statistical difference was found between the groups in terms of body mass index (p=0.009) and vitamin 25(OH)D levels (p=0.009). A very weak and positive correlation (Rho=0.015) was found between anti-Müllerian hormone and vitamin 25(OH)D levels in the group with PCOS. A weak negative correlation (Rho=-0.174) was found between anti-Müllerian hormone and vitamin 25(OH)D levels in the DOR group. However, this relationship was not statistically significant in both groups (p=0.06; p=0.128, respectively).

Conclusions: There was insufficient evidence to comment on the role of 25(OH)D in the pathogenesis of polycystic ovarian syndrome and DOR, which are at the extremes of anti-Müllerian hormone levels. This suggests that the pathophysiology of PCOS and DOR may be independent of serum vitamin 25(OH)D levels.

Keywords: Polycystic ovary syndrome, diminished ovarian reserve, anti-Müllerian hormone, vitamin 25(OH)D

Öz

Amaç: Over rezervi düşük ve polikistik over sendromlu (PKOS) infertil hastalarda anti-Müllerian hormon ile vitamin 25(OH)D düzeyleri arasındaki ilişkinin araştırılmasıdır.

Yöntem: İnfertilite polikliniğine başvuran 153 infertil hastanın verileri değerlendirildi. Androgen Excess Society kılavuzlarına göre PKOS kriterlerini karşılayan hastalar (grup 1-PKOS) ile serum anti-Müllerian hormon düzeyleri <1 ng/mL olan düşük over rezervi (DOR) (grup 2-DOR) olan hastaların serum vitamin 25(OH)D düzeyleri, anti-Müllerian hormon düzeyleri ve değişkenlerin kendi arasındaki ilişkileri karşılaştırıldı.

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Öz

Bulgular: PKOS (n=78) ve DOR (n=75) hastaları karşılaştırıldığında gruplar arasında vücut kitle indeksi (p=0,009) ve vitamin 25(OH)D düzeyleri (p=0,009) açısından istatistiksel fark bulundu. PKOS'lu grupta anti-Müllerian hormon ile vitamin 25(OH)D düzeyleri arasında çok zayıf ve pozitif korelasyon (Rho=0,015) bulundu. DOR'lu grupta anti-Müllerian hormon ile vitamin 25(OH)D düzeyleri arasında zayıf bir negatif korelasyon (Rho=-0,174) bulundu. Ancak bu ilişki her iki grupta da istatistiksel olarak anlamlı değildi (sırasıyla p=0,06; p=0,128).

Sonuç: Anti-Müllerian hormon düzeylerinin uç noktalarında yer alan PKOS ve DOR patogenezinde 25(OH)D'nin rolü hakkında yorum yapmak için yeterli kanıt yoktu. Bu, PKOS ve DOR patofizyolojisinin serum vitamin 25(OH)D düzeylerinden bağımsız olabileceğini düşündürmektedir.

Anahtar Kelimeler: Polikistik over sendromu, düşük over rezervi, anti-Müllerian hormonu, 25(OH)D vitamini

Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine pathology that occurs in approximately 6-10% of women[1]. The syndrome can cause infertility with menstrual irregularity, obesity, insulin resistance, hyperlipidemia, hyperandrogenism (male pattern hair loss, acne, and hirsutism), and anovulation manifested by oligomenorrhea[1]. Women with PCOS may also have other potential systemic diseases, such as type 2 diabetes mellitus, cardiovascular diseases, nonalcoholic steatohepatitis, sleep apnea, depression, and anxiety[1]. Therefore, lifelong follow-up for PCOS is necessary and taking precautions to protect patients from such complications is essential.

Anti-Müllerian hormone (AMH) is a structured glycoprotein hormone released by pre-antral and small antral follicles[2]. AMH levels in the reproductive period are closely related to the follicle pool that can ovulate, making it an ideal marker to assess functional ovarian reserve[3]. Women with PCOS have significantly higher serum AMH levels than healthy women[4-6]. Although AMH is not among the diagnostic criteria for PCOS because of the lack of an international standard, it is considered a prognostic marker in PCOS[7].

Recently, researchers have focused on the importance of vitamin 25(OH)D (vitamin D) not only for the musculoskeletal system but also for pathologies in the female reproductive system, diabetes mellitus, cardiovascular diseases, and infertility. Numerous studies have investigated the effects of vitamin D on the reproductive system[8-12]. Kinuta et al.[8] demonstrated that the absence of vitamin D in mutant female mice lacking the vitamin D receptor leads to infertility due to gonadal insufficiency. Xu et al.[9] detected vitamin D in the follicular fluid of macaque monkey ovarian follicles and showed that vitamin D biosynthesis occurs in the ovary and that vitamin D plays a role in folliculogenesis. Merhi et al.[10] found that vitamin D contributes to follicling maturation and steroidogenesis in granulosa cells of patients undergoing *in vitro* fertilization. Vitamin D increases the number of granulosa cells *in vitro* directly through the *AMH* gene promoter[10] and indirectly through AMH signaling[11].

Consistent with the *in vitro* data, some researchers have reported a positive correlation between vitamin 25(OH)D and AMH[12,13]. Dennis et al.[12] demonstrated that vitamin 25(OH)D could positively impact AMH production.

It is controversial whether hypovitaminosis of vitamin D contributes to the development of PCOS. There is still no consensus on the effect of vitamin 25(OH)D on AMH synthesis. Therefore, we aimed to investigate the association between serum vitamin 25(OH)D levels and AMH levels in infertile patients with diminished ovarian reserve (DOR) and PCOS, which have the two extremes of serum AMH levels.

This study aimed to investigate the relationship between AMH and vitamin 25(OH)D levels in infertile patients with low ovarian reserve and PCOS.

Materials and Methods

This retrospective cohort study was approved by the Ethics Committee of İzmir Katip Çelebi University (decision no: 585, date: 22.12.2022). Between September 2012-2022, 1453 applicants to the İzmir Atatürk Training and Research Hospital's Gynecology department were screened, and 153 infertile patients who met the study criteria were included in the study following the principles stated in the Declaration of Helsinki. The inclusion criteria included women (18 to 39 years old) with serum AMH and vitamin 25(OH)D samples for infertility. Patients with a history of ovarian surgery, ovarian cyst, premature ovarian failure, metabolic disorders related to vitamin D, and those who received hormone therapy in the last 6 months were excluded from the study.

PCOS (group-1) was defined according to the Androgen Excess Society guidelines-PCOS diagnostic criteria [presence of both criteria (1+2): (i) clinical and/or biochemical

hyperandrogenism, (ii) ovarian dysfunction, and/or polycystic ovaries]. Patients with serum AMH levels <1 ng/mL were defined as DOR (group-2)[13,14].

According to their 25(OH)D levels, the groups were further categorized as (i) those with vitamin D deficiency (25 OH-vitamin D <20 ng/mL)[15] and (ii) those without vitamin D deficiency (25 OH-vitamin D >20 ng/mL).

Measurements

Ovarian evaluation to determine if they met the polycystic ovarian criteria was performed using the 8-1 MHz multifrequency AC2541 ultrasound probe from Esaote MyLabSeven (Esaote Group, Genova, Italy) transvaginally or transabdominally.

Plasma AMH concentrations were measured in the same laboratory by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (ng/mL, Beckman Coulter, Chaska, MN, USA) suitable for all patients to reduce interlaboratory variability bias. Blood samples were taken on any day of the menstrual cycle. The mean inter- and intra-assay coefficient of variation (CV) values were 4.5% and 3.6%, respectively.

Serum 25(OH) vitamin D concentrations (ng/mL) were analyzed using the DxI 800 Beckman Coulter device (California, USA) with the chemiluminescent immuno-enzymatic method. Serum AMH and 25-OH-vitamin D concentrations were evaluated in the same blood samples on the same day.

Body mass index (BMI) between 18.5 and 23 kg/m^2 was defined as average weight and 23-24.9 kg/m^2 as overweight[16].

Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (IBM® SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software package. Descriptive statistics were used to characterize quantitative variables using mean, maximum (max), and minimum (min) values and percentages for qualitative variables. The distribution of data was assessed using Kolmogorov-Smirnov analysis to determine normality. Normal distributions were reported as mean values and standard deviations were calculated. Comparisons between groups were made using student's t-test. Pearson's chi-square test was used for the comparative analysis of qualitative variables, while Fisher's exact test was used if the sample size was small (≤5). Non-parametric continuous variables were reported as medians and compared using Mann-Whitney U tests. The interquartile range (IQR) results were also given for the values recorded as median. A p-value <0.05 was considered statistically significant. Additionally, Spearman correlation analysis was used to determine whether there was a correlation between AMH and vitamin D levels. Spearman rank correlation coefficient (Rho) was calculated, with coefficients between 0 and 0.2 interpreted as a fragile relationship, between 0.2 and 0.39 a weak relationship, between 0.4 and 0.59 a moderate relationship, between 0.6 and 0.79 a high level of relationship, and between 0.8 and 1.0 a very high relationship. If rho is negative, the relationship is inverse (as one increases, the other decreases or vise versa), while if it is positive, the relationship is in the same direction (an increase in one results in an increase in the other or vise versa).

Results

The demographic and clinical data of the patients are presented in Table 1. The mean age of the patients was 27.5 years (min=18, max=39) and the mean BMI was 23.6 kg/m^2 (min=16.5, max=34.1). The mean AMH level was 2.56 ng/dL (min=0.01, max=12.68). The mean vitamin 25(OH)D level was 18.5 ng/mL (min=1.0, max=67.0). Patients were categorized into those with vitamin D deficiency (n=96, 62.7%) and those without vitamin D deficiency (n=57, 37.3%) based on their vitamin D status. Of the patients, 51% (n=78) had DOR, while 49% (n=75) had PCOS.

Table 1. Demographic and clinical data of the patients

Variables	**Variables**
Age, years, median (IQR)	26 (11)
BMI, kg/m^2 median (IQR)	23.5 (4.1)
PCOS, n/%	75/49.0
DOR, n/%	78/51.0
AMH, ng/dL, median (IQR)	1.64 (3.40)
Vitamin 25(OH)D levels, ng/mL, median (IQR)	16 (17)
D vitamin status, n/%	
Deficiency	96/62.7
Non-deficiency	57/37.3
Blood taking season, n/%	
Spring	66/43.1
Summer	29/19.0
Autumn	20/13.1
Winter	38/24.8

IQR: inter-interval quarter, n: Number, BMI: Body mass index, AMH: Anti-Müllerian hormone

Table 2 shows a comparison of patients with vitamin D deficiency (<20 ng/mL, n=96) and those without vitamin D deficiency (≥20 ng/mL, n=57). The two groups differed significantly in terms of age (p<0.001), PCOS status (p=0.02), AMH level (p=0.02), and season of blood sampling (p<0.001). Patients with vitamin D deficiency were found to be younger and had higher AMH levels than those without vitamin D deficiency. Additionally, those with vitamin D deficiency had a higher incidence of PCOS than those without vitamin D deficiency (56.3% vs 36.8%).

Table 3 compares patients with PCOS (n=78) and those with DOR (n=75). The two groups differed significantly in terms of age (p<0.001), BMI (p=0.009), AMH and vitamin D levels (p<0.001 and p=0.009, respectively) and vitamin D status (p=0.02).

There was no statistically significant difference in the season in which blood samples were taken (p=0.261). Patients with PCOS were younger, with lower BMI, higher AMH levels, and lower vitamin 25(OH)D levels than those with DOR. The proportion of patients without vitamin D deficiency was

Table 2. Comparison of those with vitamin D deficiency (Vitamin 25(OH)D <20 ng/mL) and those without vitamin D deficiency (Vitamin 25(OH)D ≥20 ng/mL)

Variables	Vitamin D deficiency (n=96)	Vitamin D non-deficiency (n=57)	P value
Age, years, median (IQR)	24 (11)	31 (11)	**<0.001**
BMI, kg/m^2, median (IQR)	23.3 (4.1)	24.2 (3.7)	0.091
DOR, n/%	42/43.8	36/63.2	**0.02**
PCOS, n/%	54/56.3	21/36.8	-
AMH, ng/dL, median (IQR)	2.10 (3.31)	0.83 (3.29)	**0.02**
Vitamin 25(OH)D levels, ng/mL, median (IQR)	10 (8)	27 (11.5)	**<0.001**
Blood taking season, n/%	-	-	**<0.001**
Spring	50/52.1	16/28.1	**0.04**
Summer	11/11.5	18/31.6	**0.02**
Autumn	8/8.3	12/21.1	**<0.001**
Winter	27/28.1	11/19.3	**<0.001**

Bold p values indicate statistical differences

IQR: Inter-interval quarter, n: Number, BMI: Body mass index, PCOS: Polycystic ovary syndrome, AMH: Anti-Müllerian hormone

Table 3. The comparison of those with PCOS and those with DOR

Variables	DOR (n=78)	PCOS (n=75)	P value
Age, years, median (IQR)	32 (9)	22 (5)	**<0.001**
BMI, kg/m^2, median (IQR)	24.0 (4.1)	22.8 (4.2)	**0.009**
AMH, ng/dL, median (IQR)	0.32 (0.73)	3.68 (2.73)	**<0.001**
Vit D status, n/%	-	-	**0.02**
Deficiency	42/53.8	54/72.0	
Non-deficiency	36/46.2	21/28.0	
Vitamin 25(OH)D levels, ng/mL, median (IQR)	19.0 (18.0)	13.0 (14.9)	**0.009**
Blood taking season, n/%	-	-	0.261*
Spring	36/46.2	30/40.0	-
Summer	14/17.9	15/20.0	-
Autumn	13/16.7	7/9.3	-
Winter	15/19.2	23/30.7	-

*Sub-comparisons were not made because it was not significant

Bold p-values indicate the statistical difference

IQR: Inter-interval quarter, n: Number, BMI: Body mass index, PCOS: Polycystic ovary syndrome, DOR: Diminished ovarian reserve, AMH: Anti-Müllerian hormone

significantly higher in those without PCOS than in those with PCOS (28.0% vs 46.2%).

A very weak and negative correlation (Rho=-0.149) was observed between AMH and vitamin D levels. Although this relationship did not reach statistical significance, there was a trend toward significance (p=0.06) (Figure 1).

When only patients with PCOS were examined, a very weak and positive correlation (Rho=0.015) was found between AMH and vitamin D levels. However, this relationship was not statistically significant (p=0.902) (Figure 2).

When only the patient group with DOR was examined, a very weak and negative correlation (Rho=-0.174) was observed between AMH and vitamin D levels. However, this relationship did not reach statistical significance (p=0.128) (Figure 3).

Discussion

This study compared serum vitamin 25(OH)D and AMH levels in infertile women with PCOS and DOR. The findings indicated that women with PCOS were younger and had lower BMI, higher AMH levels, and lower vitamin 25(OH)D levels than women with DOR. Although not statistically significant, the study found a weak negative correlation (Rho=-0.149) between AMH and vitamin 25(OH)D levels.

The relationship between serum vitamin 25(OH)D levels and PCOS remains controversial in the literature. Mahmoudi et al.[17] and Ngo et al.[18] reported significantly higher serum vitamin 25(OH)D levels in the control group (29.32 vs 19.40 ng/mL and 79.3 vs 60.5 nmol/L) compared to PCOS. On the other hand, Xu et al.[19], Savastano et al.[20], and Mazloomi et al.[21] found significantly lower serum vitamin D levels in patients with PCOS (PCOS vs control, respectively 13.0 vs 29.5

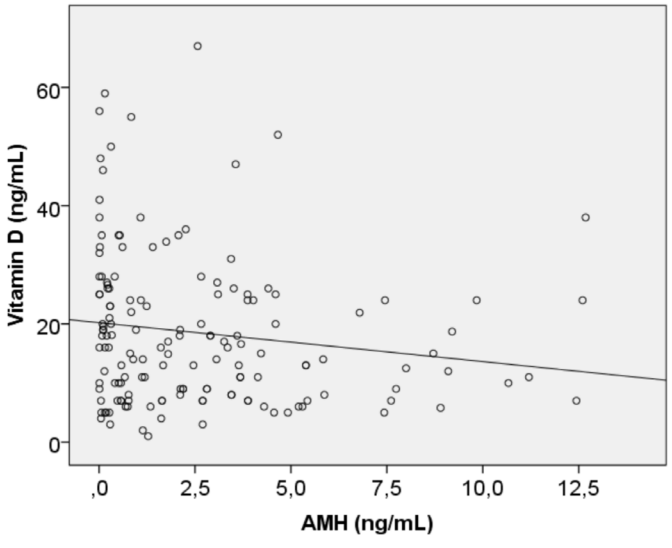

Figure 1. The correlation of vitamin D and AMH (ng/mL) in all patients

AMH: Anti-Müllerian hormone

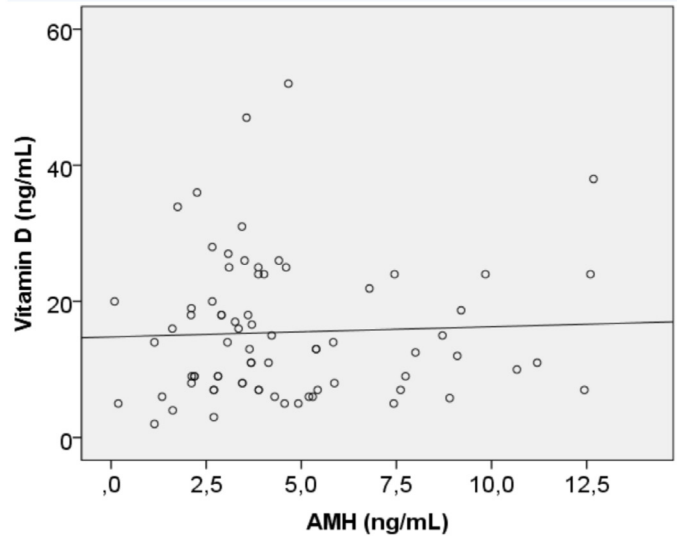

Figure 2. The correlation of AMH and vitamin D levels in the PCOS patient group

PCOS: Polycystic ovary syndrome, AMH: Anti-Müllerian hormone

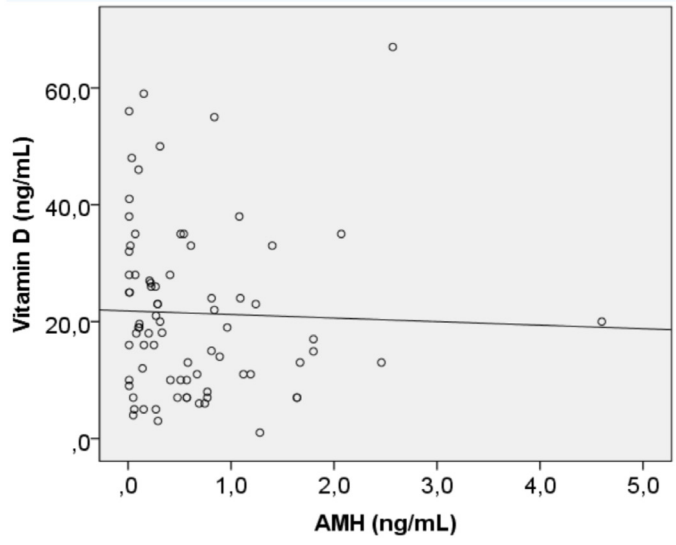

Figure 3. Correlation between AMH and vitamin D levels in the patient group with DOR

AMH: Anti-Müllerian hormone, DOR: Diminished ovarian reserve

ng/mL, 7.1 vs 31.7 ng/mL, and 12.0 vs 17.5 ng/mL). In their meta-analysis, Krul-Poel et al.[22] reported that the general average of serum vitamin 25(OH)D levels was 24.5 ng/mL in women with PCOS compared to 26.9 ng/mL in control patients, although this difference was very modest. However, He et al.[23] found no difference between their groups in their meta-analysis.

In our study, infertile patients with PCOS had lower vitamin D levels than infertile women with DOR (PCOS vs DOR: 13.0 vs 19 ng/mL). Han et al.[24] found similar serum vitamin D levels between patients with DOR and patients with normal ovarian reserve (normal ovarian reserve vs DOR: 22.2 vs 25.6 ng/mL).

Some studies[20,25] have reported that women with PCOS are more likely to be overweight or obese than those without PCOS. However, in our study, those with PCOS had a statistically lower BMI than those without PCOS, which may be associated with increased obesity prevalence with age[26].

Consistent with several studies, we found that the AMH level was significantly lower in the overweight patient group compared with the control group[27-29]. However, in our study, mean AMH levels were significantly higher in the PCOS group. Moreover, higher AMH levels were found in the group with vitamin D deficiency compared with those without vitamin D deficiency, possibly due to the higher prevalence of PCOS in the vitamin D-deficient group. The reason for the excessive production of AMH in the antral follicles of patients with PCOS has yet to be clarified.

While Irani et al.[30] have shown that vitamin D supplementation significantly reduces serum AMH levels in women with PCOS, the mechanism by which vitamin D affects AMH synthesis remains unclear. The levels of AMH in PCOS and the mechanism of action of vitamin D still require elucidation. Maintaining the biological balance between AMH and vitamin D levels appears to be a complex process.

In studies involving the infertile patient population, where patients with PCOS were excluded, no significant correlation was found between vitamin 25(OH)D and AMH values[31,32]. Drakopoulos et al.[31] concluded that routine evaluation of serum vitamin 25(OH)D levels in ovulatory infertile patients and vitamin D supplementation in those with vitamin D deficiency are unnecessary. However, they also noted that this conclusion could not be applied to patients with PCOS due to the small sample size in their study[31].

Neville et al.[32] found no correlation between vitamin 25(OH) D levels and AMH in patients undergoing *in vitro* fertilization. Chang et al.[33] found no correlation between serum vitamin 25(OH)D levels and AMH levels in healthy non-obese women. Although Tian et al.[34] found a weak but significant relationship between *in vitro* fertilization patients' vitamin 25(OH)D and AMH levels, they concluded that vitamin D does not play a significant role in embryo implantation.

Merhi et al.[35] did not find a significant relationship between vitamin 25(OH)D and AMH in young patients in their study. However, they observed a weak but significant correlation in women in the late reproductive period (age ≥40 years)[35]. Our study did not find a significant relationship between vitamin 25(OH)D and AMH values, which is consistent with other studies that included patients with PCOS[36-39]. Pearce et al.[36] reported no correlation between vitamin D and AMH levels in 340 women less than 40 years old (58 women with PCOS and 282 ovulating women) and found that seasonal variation of vitamin D did not affect AMH levels. Bakeer et al.[37] found no significant correlation between vitamin 25(OH)D and AMH levels in PCOS or healthy control groups.

Szafarowska et al.[38] found that increased AMH levels in women with PCOS appear to be associated with VDR Fok1 and Apal polymorphisms; however, they did not find a relationship with vitamin 25(OH)D levels.

Arslan et al.[39] found no difference in serum vitamin 25(OH)D and AMH levels between women with and without PCOS, and no correlation was found between vitamin 25(OH)D and AMH in the PCOS or control groups. Our findings are consistent with those of Shapiro et al.[40], who found no relationship between serum vitamin D levels and serum AMH levels in women with DOR.

There are several reasons for the conflicting results of studies examining the connection between serum vitamin 25(OH)D levels and AMH levels in PCOS. These include the lack of standardization in measuring AMH, the absence of a specific threshold value for diagnosing PCOS, and the need to determine the optimal serum vitamin 25(OH)D level in the general population.

Study Limitations

A weakness of our study is that vitamin D insufficiency [vitamin 25(OH)D <30 ng/mL] was prevalent in the majority of infertile women in our study, as vitamin D insufficiency is endemic in the Turkish female population. Due to the low

number of patients with optimal vitamin D levels [vitamin 25(OH)D >30 ng/mL], the patients were compared in terms of vitamin D deficiency [vitamin 25(OH)D <20 ng/mL]. Additionally, studies that support the effects of vitamin D on ovarian functional reserve have been conducted in healthy women of reproductive age.

Our study's strength lies in evaluating the serum vitamin D and AMH levels in the infertile patient population with PCOS and DOR, as the effects of vitamin D on ovarian reserve may differ across patient groups. Although a negative correlation was found between serum AMH and vitamin 25(OH)D levels in our study, it was not statistically significant.

Conclusion

No correlation was found between elevated serum AMH levels and vitamin D deficiency in infertile patients with PCOS and DOR. This suggests that the pathophysiology of high AMH in infertile patients with PCOS and DOR may be independent of serum vitamin 25(OH)D levels.

Further studies with standardized laboratory parameters and larger sample sizes are needed to investigate the correlation between vitamin D and AMH levels in PCOS and DOR.

Therefore, there is currently insufficient evidence to comment on the role played by vitamin 25(OH)D in the pathogenesis of PCOS.

Ethics

Ethics Committee Approval: This retrospective cohort study was approved by the Ethics Committee of İzmir Katip Çelebi University (decision no: 585, date: 22.12.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: H.Ş.S., Data Collection or Processing: M.Ş., H.Ş.S., Analysis or Interpretation: M.Ş., Literature Search: M.Ş., Writing: M.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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