Correlation of Vitamin D and Anti-Müllerian Hormone Level in Infertile Women with Polycystic Ovary Syndrome and Obesity

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Abstract

Introduction: Increasing amount of research indicates that women with PCOS are more likely to have a shortage in vitamin D with abnormally high anti-Müllerian hormone (AMH) levels. This study aims to assess the correlation between vitamin D and Anti-Mullerian Hormone (AMH) levels in infertile women with polycystic ovarian syndrome (PCOS) and obesity.

Method: This observational cross-sectional study examined all obese women with PCOS who sought infertility treatment at Dr. Mohammad Hoesin Hospital Palembang from August 2021 to November 2021. PCOS diagnosis was determined using the Rotterdam criteria. All research subjects underwent a physical examination and transvaginal ultrasound to evaluate body mass index (BMI) and polycystic ovary morphology. Blood samples were collected to evaluate their testosterone, AMH, and vitamin D levels. Statistical analysis was performed using the Spearman correlation test with IBM® SPSS Statistics version 24.

Results: Thirty infertile women with PCOS and obesity were included in the study, with average age of 31.17±4.48 years and average BMI of 33.45±2.67 kg/m2. The majority of the subjects had polycystic ovary morphology (86.7%) and oligomenorrhea (76.7%). No correlation between BMI and vitamin D as well as AMH levels was found in infertile women with PCOS and obesity. The Spearman test showed moderate negative correlation ($p = 0.011$. $r = -0.458$) between vitamin D and AMH levels in infertile women with PCOS and obesity.

Conclusion: There is a moderate negative correlation between vitamin D and AMH levels among infertile women with PCOS and obesity. Further research is required to comprehend the role of vitamin D in female fertility.

Keywords: Anti-Müllerian Hormone, Body mass index, Obesity, Polycystic Ovarian Syndrome, Vitamin D

Korelasi Vitamin D dan Kadar *Hormon Anti-Müllerian* pada Wanita Infertil dengan Sindrom Ovarium Polikistik dan Obesitas

Abstrak

Pendahuluan: Semakin banyak penelitian melaporkan bahwa wanita dengan PCOS cenderung mengalami defisiensi vitamin D dengan penignkatan kadar hormon anti-Müllerian (AMH). Penelitian ini bertujuan untuk mengkaji hubungan vitamin D dan kadar AMH pada wanita infertil dengan sindrom ovarium polikistik (SOPK) dan obesitas.

Metode: Penelitian ini merupakan studi observasional potong lintang terhadap seluruh wanita infertil dengan SPOK dan obesitas yang di RSUP Dr. Mohammad Hoesin Palembang pada bulan Agustus 2021 hingga November 2021. Diagnosis SOPK ditegakkan berdasarkan kriteria Rotterdam. Seluruh subjek penelitian menjalani pemeriksaan fisik dan ultrasonografi transvaginal untuk menilai indeks massa tubuh (IMT) dan morfologi ovarium polikistik. Sampel darah dikumpulkan dari semua wanita untuk mengukur kadar testosteron, AMH, dan vitamin D. Analisis statistik dilakukan dengan menggunakan uji korelasi Spearman menggunakan IBM® SPSS Statistics versi 24.

Hasil: Tiga puluh wanita infertil dengan SOPK dan obesitas dilibatkan dalam penelitian ini dengan usia rata-rata 31,17±4,48 tahun dan rata-rata IMT 33,45±2,67 kg/m^2. Mayoritas subjek memiliki morfologi ovarium polikistik (86,7%) dan oligomenore (76,7%). Tidak ada korelasi antara IMT dan vitamin D maupun kadar AMH pada wanita infertil dengan SOPK dan obesitas. Uji Spearman menunjukkan korelasi negatif sedang ($p=0.011.r=-0.458$) antara kadar vitamin D dan AMH pada wanita infertil dengan SOPK dan obesitas.

Kesimpulan: Kadar vitamin D berkorelasi negatif dengan kadar AMH pada wanita infertil dengan SOPK dan obesitas. Penelitian lebih lanjut diperlukan untuk memahami peran vitamin D pada kesuburan wanita.

Kata kunci: Anti-Müllerian Hormone, Indeks Massa Tubuh, Obesitas, Sindrom Ovarium Polikistik, Vitamin D

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders affecting 3–26% of women of reproductive age. The main complication of PCOS is infertility.[1,2] Currently, there is a growing focus the reproductive medicine community has placed on vitamin D supplementation. This is based on the mounting research suggesting that vitamin D may have positive effects on conception and pregnancy. Recent studies have proposed that vitamin D may have a regulatory role in female fertility, although the specific mechanism is not well understood. Rats with vitamin D deficiency experience a 75% loss in fertility, along with a 30% decrease in the number of offspring.[3] Furthermore, an increasing amount of research indicates that women with PCOS are more likely to have a shortage in vitamin D.[4] Studies have demonstrated that supplementing with vitamin D can enhance monthly regularity, reduce excessive male hormones, and improve metabolic factors associated with PCOS.[5] This suggests that vitamin D might enhance the benefits of female fertility in PCOS women.

The anti-Müllerian hormone (AMH) functions as a suppressor of FSH sensitivity in developing antral follicles. Due to the high number of follicles in their early stages of development, patients with PCOS may have abnormally high AMH levels.[6] Dennis et al.[7] have proposed that vitamin D might have a regulatory function in the generation of AMH. However, other studies did not confirm this finding.[8–10] Given the inconsistent findings and growing interest in this area, this study aims to assess the correlation between vitamin D and AMH levels in infertile women with PCOS and obesity in order to provide clarity on the role of vitamin D in female fertility in such a population.

Method

This is a cross-sectional study involving all obese women with PCOS who sought infertility treatment at Dr. Mohammad Hoesin Hospital Palembang from August 2021 to November 2021. The sampling method used was total sampling. PCOS diagnosis was determined using the Rotterdam criteria, i.e. the presence of at least two oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology.[11] Obese (body mass index >30 kg/m2) infertile women with PCOS between the ages of 18 and 45, who had been unable to conceive after a year of regular sexual intercourse with other causes of infertility excluded (fallopian tube obstruction and abnormal semen analysis) were included in the study. Women who had a previous history of endocrine or metabolic disorder, ovarian masses, endometriosis, congenital adrenal hyperplasia (CAH), androgen-secreting tumors, or Cushing's syndrome were excluded from the study. Patients who had undergone treatment for PCOS and who were taking any vitamin supplements were also excluded from the study.

All of the research subjects underwent a physical examination to calculate body mass index (BMI). Transvaginal two-dimensional probe on an ultrasonography machine (Voluson E6, GE HealthCare) was used to evaluate the polycystic ovary morphology on days 2 to 5 of the menstrual cycle. A polycystic ovary morphology is indicated when there are at least twelve follicles measuring 2–9 mm in diameter and/or an ovarian volume >10 mL. Furthermore, blood samples were collected from all the women to evaluate their testosterone, AMH, and vitamin D levels. All of the women involved in the study had vitamin D values below 50 nmol/L or 20 ng/mL, which is the recognized threshold for vitamin D deficiency by the Institute of Medicine and Endocrine Society.[12,13]

Statistical analysis was carried out using

IBM® SPSS Statistics version 24. Bivariate correlations were analyzed with Spearman correlation with a p-value of <0.05 regarded as statistically significant. Written informed consent was obtained from each participant woman before their inclusion in the study. The Health Research Ethics Committee of Dr Mohammad Hoesin Hospital Palembang (96/kepkrsmh/2021) has permitted the conduct of this study.

Results

A total of 30 infertile women with PCOS and obesity were included in the study. The sociodemographic and clinical characteristics of the subjects are listed in Table 1. The average age of the subjects was 31.17±4.48 years with an average BMI of 33.45±2.67 kg/m2. The majority of the subjects had polycystic ovary morphology (86.7%) and oligomenorrhea (76.7%).

Vitamin D and AMH levels in infertile women with PCOS and obesity are presented in Table 2.

The Spearman test showed no correlation between BMI and vitamin D as well as AMH levels in infertile women with PCOS and obesity (Table 3).

The Spearman test showed a moderate negative correlation (p=0.011. r=-0.458) between vitamin D and AMH levels in infertile women with PCOS and obesity (Table 4, Figure 1).

Table 1 Sociodemographic and Clinical Characteristics of Subjects

Sociodemographic characteristics	Mean±SD	Range (Minimum-Maximum)
Age (years)	31.17±4.48	21–43
Duration of marriage (years)	3.47±1.71	1–10
Body weight (kg)	80.23±6.63	65–93
Body height (cm)	154.90±3.84	150–1164
Body mass index	33.45±2.67	28.13–39.56
Clinical characteristics	**n**	**%**
Menstrual disturbance		
Oligomenorrhea	23	76.7
Amenorrhea	7	23.3
Hyperandrogenism	6	20
Polycystic ovary morphology	25	83.3

Table 2 Vitamin D and AMH Levels in Infertile Women with PCOS and Obesity

Laboratory results	Mean±SD	Range (Minimum-Maximum)
Vitamin D (ng/ml)	154.90±3.84	5.40–19.90
AMH (ng/ml)	4.49±1.96	0.30–10.20

Table 3 Correlation between BMI, Vitamin D, and AMH Levels in Infertile Women with PCOS and Obesity

Correlation	P value	Correlation Coefficient (r)
BMI and Vitamin D	0.809	0.046
BMI and AMH	0.926	-0.018

Table 4 Correlation between Vitamin D and AMH Levels in Infertile Women with PCOS and Obesit

Correlation	P value	Correlation Coefficient (r)
Vitamin D dan AMH	0.011	-0.458

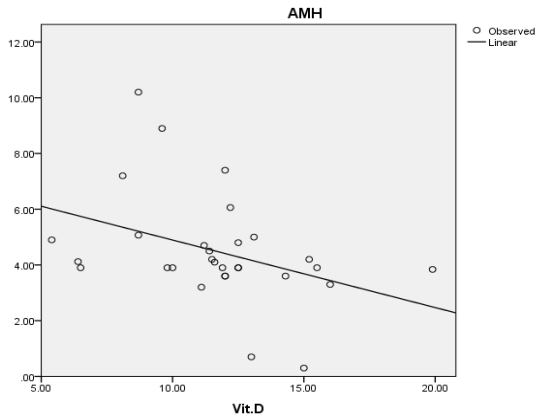

Figure 1 Scatter Plot of Vitamin D and AMH Levels in Infertile Women with PCOS and Obesity

Discussion

The average age of the subjects in this study was 31.17 with the youngest being 21 years and the oldest being 43 years. Comparison is not possible because no prior research has been done on the same population—that is, infertile women with PCOS and obesity—in this particular setting. The average BMI in this study was 33.4 kg/m^2 with the lowest BMI being 28.13 kg/m^2 and the highest being 39.56 kg/m^2. Women with irregular menstrual periods are more likely to have obesity and a higher BMI compared to women with regular cycles. Women with higher BMIs were also more likely to develop irregular menstruation and anovulatory infertility compared to those with normal body weights. The relative risk of anovulatory infertility in women of reproductive age rises at a BMI of 24 kg/m^2 and continues to rise as BMI rises.[14] This may be related to the increased production of androgens in patients with obesity. Obesity, particularly central obesity, aggravates irregular menstruation in PCOS patients because it lowers sex hormone-binding globulin levels, which can lead to more severe hyperandrogenism.[15]

In this study, the majority (76.7%) of the research subjects experienced menstrual abnormalities in the form of oligomenorrhea, i.e. menstrual cycle of more than 35 days. Previous studies report that the prevalence of oligomenorrhea is increasing from year to year throughout the world to around 12–15.3% in the general population of women of reproductive age.[14] In individuals who have PCOS, as in this study, the prevalence can increase drastically, reaching 75–85%. The presence of polycystic ovary (86.7%) in this study had a distribution similar to a previous study by Oridi and Onwuegbulam Vadumeme and Chidi, i.e. 92%.[16]

In this study, no correlation was found between BMI and vitamin D levels in infertile women with PCOS and obesity. However, previous research by Lagunova et al.[17] reported increased vitamin D levels along

with BMI increase because high-fat levels serve as a reservoir for fat-soluble vitamin D. Body fat can store about 10%-12% of vitamin D. The amount of vitamin D released from fat is inversely correlated with the amount of the vitamin in fat tissue. This biological process aims to keep the body at appropriate levels of vitamin D while shielding it from the harmful effects of the active form of vitamin D. The difference in results might be due to different populations. In our study, all of the research subjects are obese. Decreased serum vitamin D levels may be the result of sequestration and decreased biodiversity brought on by higher fat percentages in the obese population. Apart from that, there may be confounding factors that could influence vitamin D levels, such as taking vitamin D supplements or sun exposure. Vitamin D levels can also be influenced by diet; eating foods high in vitamin D, such as fish, eggs, and animal liver, can increase vitamin D levels.[18]

In this study, no correlation was found between BMI and AMH levels in infertile women with PCOS and obesity. Bernardi et al.[19] reported a significant relationship between BMI and AMH among reproductive-aged women ($r = -0.015$; $p < .0001$), but not within the BMI ≥25 cohort. AMH production may also be impacted by adiponectin, an adipokine that is less concentrated in women with higher BMI.[19] Granulosa cells have adiponectin receptors, and it is believed that signaling prevents aromatase activity. Reduced adiponectin may cause a release from adiponectin-mediated regulation, which could lead to a rise in the estrogen-to-androgen ratio and potential suppression of AMH synthesis. It has also been proposed that elevated catabolism or AMH clearance may be a factor in the decline in levels seen in women with higher BMIs. These mechanisms may be altered in obese patients with BMI ≥25, especially in the PCOS population. Independent of BMI, women with PCOS have a more inflammatory form of adiposity and decreased insulin sensitivity. As a result, inflammation, insulin signaling, and hyperandrogenism may contribute to a different effect of BMI on AMH production in PCOS women.[20] Additional elucidation of plausible pathways between serum AMH and BMI may yield significant understandings of ovarian physiology.

There was a moderate negative correlation between vitamin D and AMH levels among infertile women with PCOS and obesity in this study. Wong et al. reported a weak positive correlation ($r = 0.123$, $p = 0.009$) between vitamin D and AMH levels in 451 PCOS women after controlling for BMI.[20] Other studies reported no correlation between vitamin D and AMH levels in PCOS women.[21] The difference in findings might be due to different study populations as the previous study did not analyze the correlation in PCOS women with obesity and infertility subgroup. A previous study by Bednarska-Czerwińska et al.[22] with a similar population to our study also reported a negative correlation ($r = -0.28$, $p = 0.0391$) between vitamin D and AMH in infertile women with vitamin D levels of < 30 ng/mL, but no correlation in infertile women with normal vitamin D level. However, the study excluded patients with PCOS.

A systematic review and meta-analysis conducted by Moridi et al.[23] found that vitamin D supplements have an impact on AMH levels. However, the effects of these supplements vary depending on the ovulatory status of the women. In ovulatory women with no PCOS, it elevated serum AMH levels. In contrast, vitamin D administration reduced AMH levels in PCOS women. In a prospective trial, Irani et al.[24] reported the impact of vitamin D supplementation (50,000 IU of oral vitamin D3 for eight weeks) on AMH levels in 67 women with vitamin D deficiency (<20 ng/mL). The administration of vitamin D supplements resulted in the

restoration of normal serum vitamin D and AMH after eight weeks of treatment.

Multiple studies have reported a potential association between vitamin D deficiency and infertility in women with PCOS and obesity, in relation to reduced insulin sensitivity caused by a lack of vitamin D. Hyperinsulinemia may lead to the increase in the production of androgens as well as the decrease sex hormone-binding globulin (SHBG) concentration, leading to the development of hyperandrogenism. Excessive levels of androgens are converted into estrogen which stimulates the release of luteinizing hormone (LH) and inhibits the production of follicle-stimulating hormone (FSH) by the anterior pituitary gland, resulting in infertility. Its association with AMH levels, however, remains unclear. Multiple studies have demonstrated improvements in the clinical symptoms of PCOS after Vitamin D supplementation, including decreased AMH levels as this likely indicates an improvement in the development of ovarian follicles and ovulation.[25] This supports the idea that vitamin D might have an impact on AMH levels in PCOS.

To the best of our knowledge, this is the first study to assess the correlation between vitamin D and AMH levels among infertile women with PCOS and obesity. This study has several limitations due to its observational design and small sample size. Furthermore, it is crucial to acknowledge that all participants in this study exhibited vitamin D deficiency from the start of the study, thus constraining the extent of the findings. The highly specific population also makes comparison with earlier studies difficult. Further research is required to comprehend the role of vitamin D in female fertility. A clinical trial with a large sample size is also needed to extrapolate these findings and promote the use of vitamin D supplementation at specified doses and duration in infertile women with PCOS and obesity.

Conclusion

There is a moderate negative correlation between vitamin D and AMH levels among infertile women with PCOS and obesity. Further research is required to comprehend the role of vitamin D in female fertility.

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