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Association of Ovarian Reserves with Body Mass Index, Age and Vitamin D in Infertile Females

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ABSTRACT

Introduction

Body mass index (BMI) may modulate ovarian reserve (OR) markers, and age-related fertility decline is well-established. Vitamin D has polygenetic effects on infertility, with its higher levels suggesting a positive correlation with OR markers. This study investigates the association of OR markers (AMH and FSH) with BMI, age and vitamin D in infertile females.

Methods

An analytical study was conducted at Tribhuvan University Teaching Hospital, Nepal. The association of OR markers with BMI, age and Vitamin D level were analysed in infertile females over a year.

Results

The study includes 186 infertile females, aged between 18 to 45 years. The study found no significant correlation between the OR marker (AMH) and body mass index ($p = 0.92$) or between OR (FSH) and BMI ($p = 0.50$). However, there was a significant negative correlation between age and BMI ($p = 0.02$). There was also a significant negative correlation between age and OR (AMH) ($p = 0.04$), but not between age and OR (FSH) ($p = 0.09$). And no significant correlation between vitamin D and OR (AMH/FSH) in infertile women, suggesting that vitamin D levels do not impact OR markers.

Conclusion

The study found no significant association between OR markers, BMI, age and vitamin D in infertile women.

Keywords

Anti-Müllerian hormone; body mass index; follicular stimulating hormone; infertility; ovarian reserve; vitamin D.

INTRODUCTION

Around 8-12% of women worldwide experience infertility. The reproductive potential in female is significantly influenced by the ovarian reserve (OR).[1,2] Traditionally, age is used to determine OR, but biochemical markers and imaging-based diagnostic tests are now being used to quantify it.[3] BMI can adversely affect ovarian function and is widely linked to OR markers - Anti-Müllerian hormone (AMH) and follicular stimulating hormone (FSH).[4] AMH is more sensitive and specific, due to its gonadotropin-independent nature and less fluctuation in menstrual cycle.[5,6] However, AMH levels are affected by several other factors.[1,7,8] No defined normal cutoff exists, but >0.8–1.0 ng/ml suggests normal OR.[8]

FSH when elevated above 10 mIU/ml, indicate diminished OR.[9] AMH decreases as age increases, while FSH increases as age increases.[10] The American Society for Reproductive Medicine considers evaluation of both serum methods acceptable measures of OR.[11] Random AMH measurements predict baseline FSH levels in 6 weeks. However, measuring FSH has limitations because of time and variability caused by E2 levels.[12,13] Obesity and advanced maternal age negatively impact women's fertility, especially in older women.[14,15]

A U-shaped relationship between age and BMI is analysed, with low BMI affecting estrogen production, irregular menstrual cycles and anovulation, while excess body fat increases estrogen production.[15] The pleiotropic effect of Vitamin D in infertility has been gaining attention. Studies show a positive correlation between higher vitamin D levels and OR markers.[16] This study aims to evaluate the association among OR markers with BMI, age and vitamin D.

METHODS

This is a retrospective descriptive study conducted over a period of one year 2022/January/15 to 2023/January/14 in the infertility clinic of Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Data collection done after approval from the Institutional research Committee (IRC). Women who were diagnosed as infertile and had undergone blood investigation as per hospital protocol were included in the study. Patients' age, parity, infertility type, cause and body mass index were recorded from their record book.

Venous blood from patients was taken on the 2nd or 3rd day of their menstrual cycle to analyze hormones such as Luteinizing hormone, Follicular stimulating hormone, Estradiol, Testosterone, Thyroid function test, Prolactin were recorded in record book. After all data collection from the clinic's record book and data were analyzed using SPSS version 22.

FSH, LH levels were measured using chemiluminescence method. Serum AMH, Estradiol, Testosterone, Thyroid Function Test and Prolactin were measured by Enzyme-linked Immunosorbent Assay (ELISA). Vitamin D was measured using competitive Chemiluminescent Immunoassay (CLIA) technique.

BMI, formerly Quetelet index, measures adult nutritional status by dividing weight in kilograms by the square of the person’s height in meters. It is a key indicator of a person's health, according to WHO classification; ≤ 18.5: Underweight, 18.5–24.9: Normal weight, 25.0–29.9: Pre-obesity, 30.0–34.9:Obesity class I, 35.0–39.9: Obesity class II, Above 40:Obesity class III.

RESULTS

The study involved 186 infertile female. Most females (41.93%) fell into the 26-30 years age group. The frequency distribution of age groups is shown in Table 1. The mean body mass index (BMI) of the patients was 25.54 ± 4.55 kg/m^2, and the BMI categories are shown in Table 2.

Among the patients, 65% (n=120) had primary infertility and 35% (n=66) had secondary infertility. Regarding the pattern of menstrual cycle, 70% (n=130) patients had regular cycles and 30% (n=55) had irregular cycles. The most common cause was unexplained (49.5%), followed by male factor (27%) (Table 3).

The mean levels of OR markers, such as Anti-

Table 1. Age distribution of patients (n=186)

Age (years)	Frequency (%)
<20	10 (0.53%)
20-25	23 (12.36%)
26-30	78 (41.93%)
31-35	52 (27.95%)
36-40	28 (15.05%)
41-45	4 (2.15%)
Total	186 (100%)

Table 2. Body mass index of patients (n=186)

BMI	Frequency (%)
<18.5	6(3.22%)
18.5-24.9	77 (41.39%)
25-29.9	75 (40.32%)
30-34.9	23 (15.05%)
35-39.9	5 (2.65%)
Above 40	None
Total	186 (100%)

Table 3. Causes of infertility

Cause of Infertility	Frequency (%)
Unexplained	92 (49.5%)
Male Factor	50 (27%)
Female	36 (19.8%)
Both	8 (4.3%)
Total	186 (100%)

Table 4. Hormonal profile of patients

Hormones	Mean
AMH (IU/ml)	3.66±7.61 (range 0.01- 8)
FSH (IU/ml)	5.53±2.30
Estradiol (pg/ml)	39.84±22.84
LH (IU/ml)	4.79±4.065
TSH (mg/dl)	3.3±4.98
Prolactin (ng/ml)	18±25.986
Testosterone (mg/dl)	33.954±14.50
Vitamin D (IU/ml)	16.78±9.18

Müllerian hormone (AMH), Estradiol (E2), Follicle-stimulating hormone (FSH), and Luteinizing hormone (LH), as well as other hormonal parameters, such as Thyroid-stimulating hormone (TSH), Vitamin D, Prolactin, and Testosterone, are shown in Table 4.

The association of OR markers with BMI and age was analyzed using Pearson correlation coefficient. No significant correlation between OR (AMH) and BMI ($p = 0.9$) or between OR(FSH) and BMI ($p = 0.50$) were noted. However, there was a significant negative correlation between age and BMI ($p = 0.02$), indicating that older patients had lower BMI values.

There was also a significant negative correlation between age and OR (AMH) ($p = 0.04$), indicating that older patients had lower AMH levels. And there was no significant correlation between age and OR (FSH) ($p = 0.09$). The association of vitamin D with OR markers was also analyzed using Pearson correlation coefficient. There was no significant correlation between vitamin D and OR (AMH) ($p = 0.41$) or between vitamin D and OR(FSH) ($p = 0.87$), indicating that vitamin D levels did not affect the ovarian reserve of the patients.

DISCUSSION

The ideal body weight for females is crucial for reproductive functions, and excessive weight can increases the risk of infertility. It has been shown that the probability of pregnancy is reduced by 5% per unit of BMI exceeding 29 kg/m2.[17] Grodstein et al.revealed that impaired ovarian folliculogenesis, anovulatory infertility and high free estrogen level, were higher in women whose BMI was greater than 26.9 kg/m^2. Studies show impact of body weight on fertility in one or other way, however association of ovarian reserve and female body weight have conflicting results.[18]

Dragos et al. showed positive correlation of serum AMH with BMI, particularly in patients under 35.[19] Contradicted to it, Pereira et al. reported that BMI does not affect AMH levels and concerns on infertility in women with high BMI may be related to follicular development/oocyte maturation or endometrial disorders, rather than decreased OR.[20]

Lim et al found that AMH levels negatively correlate with BMI, TC, LDL, and HDL, suggesting lipid profile changes may influence AMH levels in women with diminished ovarian function, rather than obesity itself.[21]

In few other published data, serum and ovarian measures of decreased OR show inconsistent changes with body size because the body size may alter hormone production at the level of the ovary or increase sequestration or elimination of serum hormones. [22,23]

A study conducted by Dash et al. involving 221 infertile women found a significant negative correlation between BMI and AMH levels.The study found that higher BMI leads to lower AMH levels and higher FSH levels in women, indicating reduced ovarian reserve. [24]

Another study by Jaswa et al. had shown BMI can impact serum AMH levels in women with increasing body size, possibly due to the toxic effect of adipose tissue on ovarian granulosa cells.[25] However, this study found no significant correlation between OR markers and BMI, possibly due to the lack of significant differences in body weight among the study population.

The exact mechanisms by which BMI affects OR are not fully understood, but hypotheses suggest that adipokines produced by adipose tissue disrupt ovarian function, by alterations in follicular development, leading to diminished OR. Furthermore obesity is linked to insulin resistance and hyperinsulinemia, which can negatively impact ovarian function by disrupting hormonal balance and promoting androgen production, further affecting ovarian reserve.[14]

Women are more likely to develop obesity due to a decline in their metabolic rate, which decreases by about 2% per decade after age 18.[14] However contrary to it, this study finds older patients have lower BMI may be due to most of women were in reproductive age and not much of older aged grouped. In contrast to ours, others have shown a significant increase in the prevalence of overweight and obesity with age.[26]

Aging is the main contributor to infertility and AMH levels are negatively correlated with increasing age.[27] In current study a significant negative correlation between age and OR (AMH) ($p=0.037$) indicating that older patients had lower AMH level.The decline in female fertility is likely due to a decline in oocyte quantity and quality, which restricts natural conception after 40 years.

Previous studies have demonstrated a confounding relationship between 25OH-D and OR markers, AMH and FSH. A study published in the Journal of Clinical Endocrinology and Metabolism demonstrated that women with vitamin D deficiency had significantly lower AMH levels compared to those with sufficient vitamin D levels.[28] Another study published in the European Journal of Obstetrics, Gynecology, and Reproductive Biology in reported a positive association between vitamin D levels and OR markers.[29] Anti-müllerian hormone maintains oocyte pool by inhibiting primordial follicle recruitment and maturation through Anti-müllerian hormone receptor (AMHR-II). One study has suggested that vitamin D might suppress expression of AMHR-II, thereby decreasing the inhibitory effect of AMH and allowing follicular maturation and subsequent ovulation. In addition, a vitamin D response element in AMH gene promoter region may impact AMH production.[30] However this study lacks vitamin D association with OR markers due to small sample size.

Jukic et al. reported low 25OH-D levels associated with high FSH levels in 527 uterine fibroids patients, indicating negative impact on ovarian reserve 29 whereas, Shapiro et al. reported FSH level to be same between patients with low and normal vitamin D level. These outcome variations could be, due to different patient population differences, with variable age groups and unknown fertility status.[30]

CONCLUSION

To conclude, OR markers are not significantly associated with BMI however a significant negative association was noted with age of infertile female with BMI and AMH. No significant association was found between age and FSH. There was no significant correlation between vitamin D and OR (AMH) or between vitamin D and OR(FSH), indicating that vitamin D levels did not affect the ovarian reserve of the infertile women in this study population.

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CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

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