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Original Article

# Vitamin D and Hormonal Associations in Female Infertility: AMH and FSH Correlation

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## Abstract

**Introduction:** Infertility poses significant challenges to couples, impacting emotional well-being. Vitamin D's role in reproductive health, particularly its potential influence on Anti-Mullerian Hormone (AMH) production, remains a subject of debate. Previous studies present conflicting findings regarding the relationship between vitamin D and AMH levels. **Objectives:** This study aimed to elucidate the correlation between serum vitamin D, AMH, and Follicle-Stimulating Hormone (FSH) levels in women facing infertility. The research sought to assess variations in vitamin D, AMH, and FSH concentrations, exploring their potential roles in infertility. **Materials and Methods:** The study involved 120 infertile women aged 22-43 years. Serum samples were collected and analyzed for vitamin D, AMH, and FSH levels. Statistical analyses, including one-way ANOVA and chi-square tests, were employed to examine associations. **Results:** Among participants, 60% exhibited vitamin D deficiency, and no significant correlation was found between vitamin D levels and AMH across different age groups. The study observed variations in AMH and FSH levels, emphasizing the complex interplay in infertility. **Conclusion:** This investigation underscores the prevalence of vitamin D deficiency in infertile women and challenges the purported direct link between vitamin D and AMH. Results indicate a nuanced relationship, necessitating further research to unravel the intricate dynamics of vitamin D's impact on reproductive markers in infertility.

***Keywords:*** *Anti-Mullerian Hormone, Deficiency, Follicle Stimulating Hormone, Infertility, Reproductive Health, Vitamin D.*

## Introduction

Infertility is a reproductive system disorder that encompasses a wide range of conditions affecting an individual's ability to conceive. Female infertility is diagnosed when there is an inability to achieve a clinical pregnancy after 12 months of consistent, unprotected sexual intercourse with a healthy partner, and it may lead to heightened feelings of anxiety and depression (Yatsenko *et al*., 2019). The primary organs responsible for synthesizing Vitamin D and its metabolites are the skin, liver, and kidneys, with less than 20% originating from dietary sources (Holick *et al*., 2007). Initially, Vitamin D synthesized in the skin undergoes hydroxylation in the liver. Subsequently, the kidneys perform hydroxylation, converting 25-hydroxyvitamin D (25(OH) D) into its active form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) (von Websky *et al*., 2018). Furthermore, the active form of Vitamin D can also be locally synthesized in various tissues, including the ovaries, breasts, prostate, brain, and colon,

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through the action of 1α-hydroxylase (Lips *et al*., 2010, Dey *et al*., 2024, Hegacy *et al*., 2023, Holt *et al*., 2024).

Vitamin D deficiency is acknowledged as a possible factor in the onset of gestational diabetes mellitus, as it plays a crucial role in regulating insulin production and tissue responsiveness to insulin. The hypothesis suggests that the maternal supply of vitamin D influences early fetal development and the immune response of the fetal-placental unit. Disruption of this balance has the potential to increase the risk of preeclampsia. Additionally, the prenatal vitamin D status is significant for the long-term health of the offspring, impacting factors such as bone development, birth weight, postnatal weight, susceptibility to autoimmune diseases, and neuropsychiatric outcomes. The biologically active metabolite 1,25 (OH) 2D3 increases with advancing gestational age, although this rise can be attributed to the availability of 25 (OH) D (Von Websky *et al*., 2018).

A hypothesis posits that Vitamin D might directly impact the production of Anti-Mullerian Hormone (AMH), potentially enabling individuals with elevated Vitamin D concentrations to maintain their ovarian reserve for an extended period (Grzechocinska *et al*., 2013, Moridi *et al*., 2020, Amaresh *et al*., 2021, Holt *et al*., 2023). Research results either corroborate the notion that vitamin D could play a beneficial role in controlling AMH production (Dennis *et al*., 2012, Khudhair *et al*., 2024) or suggest that its levels do not align with ovarian reserve or ovarian response during stimulation (Fabris *et al*., 2017). Alfred Jost, a notable French endocrinologist, conducted groundbreaking studies on Anti-Mullerian Hormone (AMH), also known as Mullerian Inhibiting Substance (MIS) (Mohanasundaram *et al*., 2022). In females, the production of AMH occurs in the granulosa cells of the ovaries, whereas in males, it is produced by the Sertoli cells in the testes (Sparic *et al*., 2024, Wall *et al*., 2024). This hormone functions as a vital biomarker, significantly influencing follicular development (Peluso *et al*., 2014).

In female fetuses, the synthesis of AMH begins after 36 weeks of gestation. This hormone is solely produced by the granulosa cells within the ovary follicles and functions autonomously, independent of gonadotropins (La Marca *et al*., 2005). The secretion of AMH starts as follicles progress from the primordial state to the primary follicle stage, reaching its maximum level at the pre-antral stage. Subsequently, it diminishes as follicles grow to their ultimate size under the influence of ovarian gonadotropin (FSH) (Tran *et al*., 1977). In women with regular menstrual cycles, FSH levels tend to range from 1.4-9.9 mIU/mL during the first half of the menstrual cycle before rising up to 17.2 mIU/mL during ovulation (Shelby *et al* 2023). The threshold for serum AMH levels is 0.6 ng/mL (Buyuk *et al* 2011).

Inadequate vitamin D levels are typically defined by 25(OH)D concentrations below 20 ng/mL, while a deficiency in Vitamin D is characterized by 25(OH)D concentrations falling between 20 and 30 ng/mL (Haimi *et al*., 2017). The prevalence of Vitamin D depletion varies widely in Europe, ranging from 8% to as high as 90%, and in North America, it spans from 14% to 89% (Van Schoor *et al*., 2017). Notably, insufficient levels of vitamin D have been linked to an increased risk of various autoimmune conditions, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus, as well as susceptibility to infections (Aranow *et al*., 2011). Moreover, it is associated with conditions such as type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular disease (CVD) (Anagnostis *et al*., 2010). Recent studies have also underscored the potential influence of vitamin D on human infertility (Cheng *et al*., 2020, Karimi *et al*., 2012). This is primarily attributed to the presence of both the receptor for vitamin D and CYP27B1 in various reproductive system tissues in both sexes (Anagnostis *et al*., 2013).

AMH emerged as a focal gene in the regulation of vitamin D, as determined through complementary deoxyribonucleic acid (cDNA) microarray analysis of a prostate cancer cell line (Krishnan *et al*., 2007). In vitro investigations demonstrated an elevated expression of AMH mRNA in response to Vitamin D. Researchers identified a functional VDR element within the human AMH promoter, affirming the direct impact of Vitamin D on AMH expression (Jeon *et al*., 2024). Additionally, Vitamin D appears to modulate AMH, FSH, and mRNA, potentially influencing the follicle selection process (Malloy *et al*., 2009, Han *et al*., 2022, Rogenhofer *et al*., 2022).

Currently, a considerable debate exists in academic literature concerning the impact of Vitamin D on AMH production and its implications for fertility. Consequently, we undertook this investigation to examine the range of Vitamin D levels in infertile females and evaluate the correlation between serum AMH and Vitamin D status in fertile ovulatory females.

The aim of this clinical research was to deepen our comprehension of the correlation between serum Vitamin D levels and the concentrations of AMH and FSH. Our objective was to identify variations in vitamin D, AMH, and FSH concentrations and subsequently evaluate their potential roles in infertility.

## Material and Methods

This research involved 120 women of reproductive age facing infertility, specifically aged between 22 and 43 years. Participants were recruited from the Obstetrics and Gynaecology (OBG) department of Mamata Academy of Medical Sciences and General Hospital, as well as the Krishna Leela Fertility Centre, Madhapur, Hyderabad, during the years 2022 and 2023 for infertility treatment purposes. Infertility in this study was defined as the absence of pregnancy after 12 months of unprotected intercourse following marriage. The enrolment of study participants strictly adhered to predefined inclusion and exclusion criteria, and informed consent was obtained from all participants.

*Sample size calculation:*

Calculation for the sample size was performed considering the prevalence of vitamin D deficiency among infertile women as 64% from the study by Lata *et al*., 2017 using the below formula.

$$n = \frac{z^2pq}{d^2}$$

z = 1.96
P = prevalence of vitamin D deficiency in infertile women 64%
Q = 1-p i.e 36%
d = relative precision, 15% of p, 9.6

$$n = \frac{1.96 \times 1.96 \times 64 \times 36}{9.6 \times 9.6}$$

n= 96 + 10% of n (with allowable error of 10%)
n=106

The calculated sample size is 106 and the obtained sample was 120.

The data were inputted into Microsoft Excel and analyzed using SPSS version 20. Mean and standard deviations were computed, the chi-square test was utilized to examine the association between AMH and FSH, and the one-way ANOVA test was applied to compare the means of Age, AMH, and FSH across different Vitamin D levels

*Inclusion Criteria:*

Women facing infertility with unexplained causes, aged between 22 and 43 years

*Exclusion Criteria:*

History of smoking (tobacco use), oral contraceptive pill, endometriosis, thyroid disorders, autoimmune disease, tubal factor, male factor, or polycystic ovarian syndrome.

*Biochemical Analysis:*

Vitamin D levels were measured using a competitive chemiluminescent immunoassay, as per the manufacturer's guidelines. Plasma AMH levels were measured using Enzyme linked immunosorbent assay (ELISA), blood sample was collected randomly at any time in the menstrual cycle. FSH levels were estimated using Enzyme linked immunosorbent assay (ELISA), blood sample was collected on second or third day of the menstrual cycle.

## Results:

**Table 1:** Baseline Particulars of the patients (n=120)

| Patient characteristics | Mean ± SD |
|---|---|
| Age (years) | 30.6 ± 5.18 |
| Vitamin D (ng/mL) | 18.85 ± 8.239 |
| AMH (ng/ml) | 3.5 ± 3.242 |
| FSH (mIU/ml) | 16.812 ± 12.267 |

The average age of the patients in the context of this study was 30.6 years with standard deviation of 5.18 years, the mean levels of Vitamin D in the patients was 18.85 ng/ml with standard deviation of 8.239 ng/ml, the mean AMH levels in the patients was 3.5 ng/ml with standard deviation of 3.242 ng/ml and the mean FSH in the patients was 16.812 mIU/ml with standard deviation of 12.267 mIU/ml

**Table 2:** Descriptive Statistics of Vitamin D

| Vitamin D | Mean ± SD | Frequency (n) |
|---|---|---|
| Deficiency: < 20 ng/ml | 13.26 ± 3.807 | 72 |
| Insufficiency: 20 - 30 ng/ml | 24.49 ± 3.094 | 34 |
| Sufficiency: 30 - 100 ng/ml | 33.93 ± 4.085 | 14 |

Among the 120 infertile women, 72 exhibited Vitamin D insufficiency (<20 ng/ml) with a mean value of 13.26 ng/ml and a standard deviation of 3.807 ng/ml. Thirty-four women demonstrated Vitamin D deficiency (20-30 ng/ml) with a mean value of 24.49 ng/ml and a standard deviation of 3.094 ng/ml. Only 14 women displayed normal levels of Vitamin D (sufficiency, 30-100 ng/ml) with a mean value of 33.93 ng/ml and a standard deviation of 4.085 ng/ml.

**Table 3:** Descriptive Statistics of AMH

| AMH | Mean ± SD | Frequency (n) |
|---|---|---|
| Optimal fertility: 4.0 - 6.8 ng/ml | 5.323 ± 0.856 | 31 |
| satisfactory fertility: 2.2 - 4.0ng/ml | 2.838 ± 0.524 | 30 |
| Low fertility: 0.3 - 2.2 ng/ml | 1.269 ± 0.443 | 40 |
| Very Low/ Undetectable: 0.0 - 0.3ng/ml | 0.086 ± 0.062 | 8 |
| high Level: > 6.8 | 11.574 ± 3.984 | 10 |

Among the 120 infertile women, 31 demonstrated an optimal fertility rate (AMH: 4.0-6.8 ng/ml) with a mean value of 5.323 ng/ml and a standard deviation of 0.856 ng/ml. Thirty women exhibited a satisfactory fertility rate (AMH: 2.2-4.0 ng/ml) with a mean value of 2.838 ng/ml and a standard deviation of 0.524 ng/ml. Forty women displayed a low fertility rate (AMH: 0.3-2.2 ng/ml) with a mean value of 1.269 ng/ml and a standard deviation of 0.443 ng/ml. Eight women presented a very low fertility rate (AMH: 0.0-0.3 ng/ml) with a mean value of 0.086 ng/ml and a standard deviation of 0.062 ng/ml. Additionally, 10 women exhibited high AMH levels (>6.8 ng/ml) with a mean value of 11.574 ng/ml and a standard deviation of 3.984 ng/ml.

**Table 4:** Descriptive Statistics of FSH

| FSH (Follicular Phase) | Mean± SD | Frequency (n) |
|---|---|---|
| >3.5 m IU/ml | 1.5058 ± 0.0199 | 16 |
| 3.5 - 12.5 mIU/ml | 8.4908 ± 2.6553 | 34 |
| < 12.5 mIU/ml | 24.1568 ± 10.4794 | 70 |

Among the 120 infertile women, 16 demonstrated reduced serum FSH levels (>3.5 mIU/ml) with a mean value of 1.5058 mIU/ml and a standard deviation of 0.0199 mIU/ml. Thirty-four women exhibited normal FSH levels in serum (3.5-12.5 mIU/ml) with a mean value of 8.4908 mIU/ml and a standard deviation of 2.6553 mIU/ml. Seventy women displayed high FSH levels in serum (<12.5 mIU/ml) with a mean value of 24.1568 mIU/ml and a standard deviation of 10.4794 mIU/ml.

**Table 5:** Mean Vitamin D levels in different age groups

| Age | Vitamin D - Mean ± SD | Frequency (n) |
|---|---|---|
| <25YRS | 16.59 ± 8.111 | 11 |
| 26-35YRS | 18.35 ± 7.449 | 88 |
| >35YRS | 21.60 ± 10.701 | 21 |

Out of 120 infertile women, 11 women are with age <25 years showed mean Vitamin D value of 16.59 ng/ml and standard deviation of 8.111 ng/ml, 88 women are with age between 26-35 years showed mean Vitamin D value of 18.35 ng/ml and standard deviation of 7.449 ng/ml, and 21 women are with age >35 years showed mean Vitamin D value of 21.60 ng/ml and standard deviation of 10.701 ng/ml.

**Table 6:** Comparison of Mean Age, AMH and FSH with Vitamin D

| Variables | Vitamin D | | | ANOVA-one way | |
|---|---|---|---|---|---|
| | <20 (n=72) | 20-30 (n=34) | >30 (n=14) | p-value | F Value |
| **AGE** | 30.17±4.72 | 31.20+5.67 | 31.38+6.23 | 0.535 | 0.629 |
| **AMH (ng/ml)** | 3.59±3.48 | 3.783+3.06 | 2.286+2.04 | 0.347 | 1.06 |
| **FSH** | 16.99±13.13 | 15.64+11.11 | 18.83+10.51 | 0.716 | 0.335 |

The ANOVA-one way test results in Table 6 shows an insignificant difference in the mean age, mean AMH and mean FSH concentrations in various vitamin D levels.

**Table 7:** Association between AMH and FSH (n=120)

| variables | | AMH | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Optimal fertility: 4.0 - 6.8 ng/ml** | **satisfactory fertility: 2.2 - 4.0ng/ml** | **Low fertility: 0.3 - 2.2 ng/ml** | **Very Low/ Undetectable: 0.0 - 0.3ng/ml** | **high Level: > 6.8** | | |
| **FSH** | >3.5 mIU/ml | 1 | 3 | 2 | 4 | 6 | 16 | **P value = 0.000** $X^2$ = **33.340** |
| | 3.5 - 12.5 mIU/ml | 0 | 10 | 7 | 13 | 4 | 34 | |
| | < 12.5 mIU/ml | 8 | 27 | 21 | 14 | 0 | 70 | |
| **Total** | | 9 | 40 | 30 | 31 | 10 | 120 | |

A statistically significant distinction ($p < 0.05$) was identified in the levels of serum AMH and FSH.

## Discussion

In our investigation, it was observed that only 11.67% of infertile females displayed normal serum Vitamin D levels. The prevalence of deficiency and insufficiency in serum Vitamin D levels varied from 60% to 88.33% in women experiencing fertility issues. Dressler *et al*. conducted research revealing that a substantial percentage, ranging from 81.3% to 98.2%, of women with impaired fertility exhibited deficient or insufficient Vitamin D levels (Dressler *et al*., 2016). Lata *et al*. (2017) reported an incidence of Vitamin D insufficiency (VDD) at 64.28% among infertile females. Our findings are consistent with these results, though with slight variations possibly due to differences in population and geographical factors.

Vitamin D, often referred to as the "anti-ricketic factor" or sunshine vitamin, is minimally influenced by dietary intake unless vitamin D supplements are taken (Dixon *et al*., 2009). Surprisingly, in tropical regions with abundant sunlight for endogenous vitamin D synthesis, insufficiency of Vitamin D (VDD) prevails at a rate of 50% to 90% across all age groups (Mehlawat *et al*., 2014). Importantly, there is no significant age-related or infertility-associated disorder-related variation in Vitamin D levels (Dressler *et al*., 2016). In a separate investigation, the prevalence of Vitamin D deficiency (VDD) was notably higher in the subfertility group compared to the control group (59.0% versus 40.4%; $P < 0.01$) (Al-Jaroudi *et al*., 2016).

There is a singular study highlighting a direct association between vitamin D and serum Anti-Müllerian Hormone (AMH) levels (Dennis *et al*., 2012). According to a study, vitamin D supplementation has been suggested to reduce excessive Anti-Müllerian hormone (AMH) production, thereby enhancing follicular sensitivity to follicle-stimulating hormone (FSH) and restoring normal ovulation (Irani *et al*., 2014). An observational study found a weak and negligible adverse correlation between serum vitamin D and AMH in young individuals. However, in women aged 40 years or older, there existed a weak and potentially favorable association between AMH and vitamin D. The current literature lacks a definitive and consistent pattern regarding how vitamin D might impact AMH production or serum levels. In our prospective study involving women of childbearing age, the key discovery is that serum vitamin D levels appear to lack a significant relationship with AMH levels. Similar results were reported by Merhi *et al*., who found no correlation between serum vitamin D and AMH levels in women aged 35 to 40 years (Lata *et al*., 2017 & Merhi *et al*., 2012).

Bednarska research uncovered an overall nonsignificant unfavorable linear association between levels of serum AMH and total vitamin D (Bednarska *et al*., 2019, Bacanakgil, *et al*., 2022). In Liu's investigation, a negative correlation was identified between Serum Vitamin D levels and AMH; however, this relationship did not reach statistical significance (Liu *et al*., 2019).

In Shapiro's study, there was no variation in AMH and FSH levels between women with Vitamin D deficiency (VDD) and those with normal levels. This lack of association was further affirmed by multivariate linear regression analysis of log-transformed AMH and FSH with 25OH-D levels, adjusting for confounders (Shapiro *et al*., 2018). Notably, no significant correlation between 25(OH)D and AMH was observed in the studies conducted by Lata *et al*.(2017), Neville *et al*.(2016), and Drakopoulos *et al*. (2017), similarly, our study also revealed no significant correlation between Vitamin D and AMH.

## Conclusion

In the group of women experiencing infertility, 60% displayed a prevalence of Vitamin D deficiency. There was no apparent correlation identified between Vitamin D deficiency and AMH levels in infertile women across different age groups. The significant occurrence of Vitamin D deficiency in women facing fertility challenges raises concerns. Urgent prospective studies are required to establish any potential causal links and explore the potential therapeutic benefits of Vitamin D supplementation in this specific demographic.

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## Conflict of Interest:

There is no conflict of interest with anybody or organization.

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