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Assessment of vitamin D levels in infertile females - a tertiary care hospital experience

Natasha Bushra^{1*}, Tahira Nasrin², Asifa Sarwar³

ABSTRACT

Background and Objective: Vitamin D deficiency emerges as a significant player in shaping reproductive health challenges including the ones with conception and fertility. The present study aims to ascertain the prevalence of vitamin D deficiency in the context of female infertility in the local population.

Methods: This cross-sectional study was conducted in the Obstetrics and Gynecology Department at Services Hospital Lahore, Pakistan, from May 30, 2021, to November 30, 2021. A total of 96 sub-fertile females, 20-40 years of age were recruited for the study after taking detailed history followed by clinical examination, and transvaginal ultrasound. The required information regarding body mass index (BMI), type of infertility, and socio-economic status were correlated with the laboratory assessment of serum vitamin D levels. Data were analyzed statistically using the chi-square test keeping p -value <0.05 as significant.

Results: The mean age of the patients was 29.43 ± 3.35 years, and the mean vitamin D level recorded was 19.03 ± 14.30 ng/ml. Notably, 97.9% of primary infertile females compared to 29.2% of secondary infertile patients exhibited vitamin D deficiency (p -value = 0.003). The deficient levels of Vitamin D were associated with the age, BMI, and socioeconomic status of these females.

Conclusion: Females with primary infertility have a notable Vitamin D deficiency compared to the ones with secondary infertility. Additional studies are pressingly needed to confirm a causal relationship and to investigate the potential therapeutic benefits of vitamin D supplementation.

Keywords: Females, infertility, Vitamin D, deficiency, body mass index.

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Correspondence to: Natasha Bushra

*Assistant Professor, Department of Obstetrics and Gynecology, Post Graduate Medical Institute, Lahore, Pakistan.

Email: natashausman5@hotmail.com

Full list of author information is available at the end of the article.

Introduction

The impact of infertility is multifaceted, encompassing emotional, financial, and social dimensions. World Health Organization (WHO) defines infertility as the incapacity of a reproductive-age couple to achieve pregnancy within 12 months or more of unprotected sexual intercourse¹. It can manifest as primary (no prior conception) or secondary (failure to conceive after a previous pregnancy without contraceptive use). Globally, around 10%-15% of couples experience infertility, with secondary infertility surpassing primary cases^{1,2}. In Pakistan, the prevalence stands at 21.9%, with 3.9% attributed to primary infertility and 18% to secondary infertility³.

The repercussions of infertility extend beyond the physical realm, affecting psychological, economic, and social well-being, particularly for females. The challenges individuals

and couples face underscore the need for comprehensive support systems and an understanding of the intricate ways infertility influences overall well-being⁴. Studies^{5,6} unveil that women undergoing infertility often face emotional harassment within marital homes, taking various forms such as verbal abuse, stigmatization, negative attitudes, physical abuse, and denial of basic needs and healthcare.

Calcium signaling, pivotal from fertilization through development, implantation, and organ differentiation, intersects with infertility. Vitamin D, a regulator of these signaling processes, plays a vital role. Infertility rates rise in the presence of vitamin D deficiency, emphasizing its importance in reproductive health⁷. Vitamin D maintains the stability of calcium and redox signaling pathways critical in the development of reproductive processes such as endometrial receptivity⁸. It influences reproductive

functions in both genders, impacting *in vitro* fertilization (IVF) outcomes, features of polycystic ovarian syndrome (PCOS), and endometriosis in women⁹. Adequate vitamin D levels enhance embryo implantation rates and follicular development in IVF, and its deficiency is linked to the metabolic and endocrine features of PCOS and the inflammatory mechanisms in endometriosis. Vitamin D deficiency is more common in women with PCOS who are experiencing infertility compared to the general population. This deficiency is linked to various aspects of PCOS, including insulin resistance, hormonal imbalances, and metabolic issues, which can further complicate fertility problems¹⁰.

In the United States of America (USA), vitamin D deficiency is reported to affect 20%-48% of the adult population while in women with PCOS and infertility, the prevalence is significantly higher, ranging from 67%-85%¹¹. In Pakistan, a cross-sectional survey was conducted with 27,880 individuals referred from the general out-patient-department (OPD) to do diagnostic research and reference laboratory (DDRRL) units at Dow University of Health Sciences (DUHS) Karachi; the status of vitamin D indicates 31.2% insufficiency, 53.5% deficiency, and 15.3% within the normal range¹². Additionally, vitamin D plays a role in sperm quality in men, affecting overall fertility. Therefore, the high prevalence of vitamin D deficiency in the population can lead to increased rates of infertility and complicated efforts to conceive¹³.

While numerous studies have reported an association between vitamin D deficiency and infertility, a notable gap still exists in our local population. The absence of empirical evidence regarding the extent of this issue in our local female population necessitated this study with an aim to determine the serum levels of Vitamin D in infertile female patients and find an association with their body mass index (BMI) and socioeconomic status.

Methods

This cross-sectional study was conducted in the Obstetrics and Gynecology Department, Unit II at Services Hospital Lahore, Pakistan, spanning from May 30, 2021, to November 30, 2021, following ethical approval from the institutional committee. A total of 96 women presenting in Gynae outdoors for the treatment of their infertility were included in the study. According to the standard guidelines, they were diagnosed to be sub-fertile according to their history of inability to conceive for the last 1 year with regular intercourse. Patients were categorized as primary or secondary infertile according to the WHO criteria¹. The cause of infertility was ascertained after detailed history, clinical examination, and transvaginal ultrasound findings. Socioeconomic status was assigned as poor (income < 50,000/month), middle (100-250,000/months), and upper (> 300,000/month) to all recruited

patients. All infertile women aged 20-40 years with who gave written informed consent were included in the study. Females if receiving pharmacological vitamin D or calcium supplementation before the date of 25 (OH)D concentration measurement, any history of malignancy, hypertension, diabetes, need for chronic medical treatments, autoimmune disorders, and any disorder that may impact on calcium or vitamin D metabolism, such as bone, parathyroid gland, kidney, and liver disorders were excluded. The sample size was calculated as $n = 96$ with a 95% confidence level, 9.5 % margin of error, and the expected percentage of Vit D deficiency in female infertility as 67%¹⁰. using www.raosoft.com. The sampling technique was non-probability purposive sampling. All patients underwent serum vitamin D level assessments from the quantitative detection of a total of 25 (OH)D levels using a commercially available kit based on a chemiluminescence technology. According to WHO recommendations, a 25 (OH)D value < 20 ng/ml was considered deficient and a value ≥ 20 ng/ml was normal¹⁴. The required information regarding age, BMI, type of infertility, socio economic status, and vitamin D levels was collected on a predesigned proforma.

Statistical analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS) version 23. Mean and standard deviations were calculated for quantitative variables, i.e., age, BMI, and vitamin D levels. Data were stratified for age, BMI, type of infertility, and socio-economic status. p values < 0.05 were considered as statistically significant.

Results

The mean age of the patients was 29.43 ± 3.35 years. The mean BMI of the patients was 25.32 ± 2.48 kg/m². According to this study, 43 (45.26%) patients were poor, 49 (51.58%) patients belonged to the middle class and 3 (3.16%) patients belonged to upper-income class. The mean vitamin D level of the patients was 19.03 ± 14.30 ng/ml with minimum and maximum levels of 1.20 and 86 ng/ml respectively as shown in Table 1. Vitamin D deficiency (defined as serum levels below 20 ng/ml)¹⁴ was observed in 61 out of 96 women, accounting for 63.54%.

The study population was evenly divided, with 48 women experiencing primary infertility and 48 women experiencing secondary infertility. Vitamin D deficiency was identified in 97.9% of primary infertile patients compared to 29.2% in secondary infertile patients, demonstrating statistical significance (p -value = 0.003).

The mean duration of primary infertility was 3.8 ± 2.1 years, with a range from 2 years to 5 years. The mean duration of secondary infertility was 4.5 ± 2.7 years, with a

Table 1. Baseline characteristics of study population.

Characteristics Total N (%)	Mean	SD	Minimum	Maximum
Maternal age (years)	29.43	3.35	22.00	40.00
BMI	25.32	2.48	18.00	30.00
Vitamin D level (ng/ml)	19.03	14.30	1.20	86.00
Type of infertility				
Primary infertility	17.5 ± 12.7	50.21	1.20	65
Secondary infertility	18.6 ± 12.8	67.36	2.5	84

Table 2. Comparison of vitamin D deficiency in multivariable analysis.

Variables		Vitamin D deficiency		Total	p value
		Yes	No		
Age (years)	≤30	47 71.2%	19 28.8%	66 100.0%	0.021
	>30	14 46.7%	16 53.3%	30 100.0%	
BMI (Kg/m ²)	≤ 25	34 79.1%	9 20.9%	43 100.0%	0.004
	>25	27 50.9%	26 49.1%	53 100.0%	
Type of infertility	Primary	47 97.9%	1 2.1%	48 100.0%	<0.001
	Secondary	14 29.2%	34 70.8%	48 100.0%	
Socioeconomic status	Poor	34 79.1%	9 20.9%	43 100.0%	0.003
	Middle	25 51.0%	24 49.0%	49 100.0%	
	Upper	1 33.3%	2 66.7%	3 100.0%	

range from 3 years to 10 years. The most common reason for secondary infertility included PCOS, affecting 20 out of 48 women with secondary infertility. Tubal Factor Infertility was identified in 10 females, often due to previous pelvic inflammatory disease or endometriosis. Uterine factors including fibroids and adhesions were reported in 8 women while unexplained reason was a contributing factor in 6 females. Table 2 illustrates a noteworthy status of vitamin D deficiency among patients based on age groups. For those aged ≤ 30 years, 71.2% exhibited vitamin D deficiency, whereas among patients aged >30 years, the prevalence was 46.7% (*p*-value = 0.021). Similarly, in the context of BMI, patients with a BMI ≤ 25 kg/m² had vitamin D deficiency in 79.1% of cases, contrasting with patients with a BMI >25 kg/m², where the frequency was 50.9% (*p*-value = 0.004). Finally, the stratification between primary and secondary infertility

revealed notable differences. Vitamin D deficiency was identified in 97.9% of primary infertile patients compared to 29.2% in secondary infertile patients (*p*-value = 0.003).

Discussion

Vitamin D treatment has demonstrated its efficacy by influencing cellular processes, such as the downregulation of follicle-stimulating hormone receptors and the role of receptors controlling antimullerian genes¹⁵. This is associated with a rise in the production of progesterone and 3β-hydroxysteroid dehydrogenase. This intervention showcases favorable effects on metabolic dysregulations in PCOS marked by a profound effect on androgen levels, potentially fostering a healthier ovarian physiology¹⁶. The prevalence of vitamin D deficiency and its effect on overall global health is a matter of concern, affecting an estimated

1 billion people worldwide¹⁷. Within the scope of this study focusing on infertility in females, vitamin D deficiency was identified in 63.54% of patients. In order to look at the relationship of pregnancy rate with vitamin D levels, Rudick et al.¹⁸ conducted a retrospective cohort research involving 18 infertile women undergoing IVF. Remarkably, the investigators discovered a correlation between declining vitamin D levels and a linear fall in pregnancy rate.

Examining related studies, Mogili et al.¹⁹ conducted research involving 256 infertile women with PCOS. Their findings revealed a deficiency of vitamin D, observed in 70.3% of the participants, with 20.3% categorized as having insufficiency of vitamin D and only 9.4% of them having normal vitamin D levels. Additionally, 31.25% of the women exhibited signs of metabolic syndrome.

The median serum 25-hydroxyvitamin D concentration undergoes a reduction in the primary trimester of the calendar year, culminating in a subsequent increase in the prevalence of deficiency thus underscoring a significant impact of seasonality on vitamin D status²⁰. It is noteworthy that this deficiency has been linked to various gynecological issues. Within the cohort of women experiencing infertility, the documented frequency of Vitamin D deficiency spans from 20% to 66.8%, manifesting variances across diverse nations²¹. In women with PCOS experiencing infertility, the prevalence, however, is notably higher, ranging from 67% to 85%²². Basile et al.²³ in their study, arrived at the conclusion that Vitamin D deficiency is widespread, impacting both fertile and infertile women. This deficiency is linked to various adverse outcomes in conditions associated with infertility. Authors, in their systematic review, revealed the presence of vitamin D receptors and metabolizing enzymes in the reproductive tissues of both males and females. They posited that vitamin D could potentially exert an influence on the synthesis of sex hormones, specifically estradiol and progesterone, in women of good health, with heightened concentrations of 25-hydroxyvitamin D potentially being linked to the presence of endometriosis²⁴.

Serum 25 (OH)D levels are highly deficient in women seeking medical help for couple's infertility. Dhamayanti et al.²⁵ in their study, concluded that there is a high prevalence of hypovitaminosis D among women of childbearing age. Evidence from observational studies indicates an important role of vitamin D in IVF success, which is probably mediated through vitamin D effects on endometrium²⁶. Research findings indicate seasonal fluctuations in circulating 25 (OH) D levels among a homogeneous cohort of women seeking medical assistance for couple's infertility in northern Italy. Ott et al.²⁷ demonstrated in a prospective cohort study that BMI and 25 (OH)D deficiency served as significant predictive parameters in 91 anovulatory infertile women with PCOS

in 2012. They noted that 25 (OH)D levels below 10 ng/ml reduced the likelihood of follicle development by 67% and the probability of becoming pregnant by 76%.

Our finding is also similar to the study conducted that also concluded major implications of vitamin D deficiency both for infertile patients and in patients undergoing IVF²⁸. We noticed that both groups including primary and secondary infertility exhibited significant deficiencies, but those with secondary infertility had marginally higher levels, possibly due to residual effects from prior pregnancies and lactation.

Although infertility among women is a multifactorial condition and might be attributed to various causes, in 50% of cases, the clear etiology is unknown. However, among conditions of infertility in which the etiology results are not clear, an increased frequency of abnormalities in the immune system has been reported²⁹. We described that having vitamin D deficiency is associated with females diagnosed with primary infertility. Our results are mainly in line with a Brazilian study³⁰ in which low vitamin D levels were independent risk factors for primary infertility in women but a recent meta-analysis on the role of vitamin D on reproductive outcome concluded that a well-designed randomized controlled trial with a large sample size are required to evaluate the effect of vitamin D supplementation on female fertility.

Conclusion

Vitamin D deficiency in the local population is associated with female infertility, particularly in cases with primary infertility, and exhibits a significant relationship with the age and BMI of these infertile females. Therefore, Vitamin D could serve as a promising therapeutic option if thoroughly investigated within the infertile female population.

Limitations of the study

Due to limited existing literature on this subject, it is recommended that future research trials should explore this topic with larger sample sizes and the role of therapeutic vitamin D deficiency. One limitation of our study is that we did not explore the association of each cause of secondary infertility with vitamin D deficiency. Additionally, emphasizing community-based studies over hospital-based studies is suggested for a more comprehensive understanding of the implications.

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List of Abbreviations

WHO World Health Organization
BMI Body mass index

IVF In vitro fertilization
PCOS Polycystic ovarian syndrome

Conflict of interest

None to declare.

Grant support and financial disclosure

None to disclose.

Ethics approval

The study was approved by the Institutional Review Committee of Services Institute of Medical Sciences, Lahore, Pakistan, vide Letter No. IRB/2021/880/SIMS dated 5th October 2021.

Authors' contributions

NB: Concept and design of study, acquisition, and analysis of data, drafting of manuscript, reviewing it critically for important intellectual content.

TN: Concept and design of study, acquisition, and analysis of data, drafting of manuscript.

AS: Acquisition and analysis of data, drafting of manuscript

ALL AUTHORS: Approval of the final version of the manuscript to be published.

Authors' Details

Natasha Bushra¹, Tahira Nasrin², Asifa Sarwar³

1. Assistant Professor, Department of Obstetrics and Gynecology, Post Graduate Medical Institute, Lahore, Pakistan
2. Senior Registrar, Department of Obstetrics and Gynecology, Services Hospital, Lahore, Pakistan
3. Postgraduate Resident, Department of Obstetrics and Gynecology, Services Hospital, Lahore, Pakistan

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