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ASSOCIATION OF VITAMIN D DEFICIENCY AND FEMALE INFERTILITY

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ABSTRACT

AIM: To study the association of Vitamin D deficiency with infertility in women and to know the correlation of Vitamin D levels with hormonal levels of TSH, FSH, LH and Prolactin in infertile patients. **METHODS:** The observational case-control study was conducted with 120 women of 18–40-year age group consisting of 60 infertile women as cases and 60 fertile women as controls visiting the Gynaecology OPD. Vitamin D levels in both case and control groups were estimated and compared. Infertile cases were categorised according to the underlying cause of infertility and vitamin D levels in each underlying cause of infertility were compared with vitamin D levels in fertile controls. Blood samples of infertile cases were analysed for TSH (thyroid stimulating hormone), FSH (follicle stimulating hormone), LH (luteinizing hormone) and Prolactin levels and any correlation of these parameters with vitamin D levels were taken note of. **RESULTS:** Vitamin D deficiency was found to be 65.0% in our study population. Vitamin D deficiency was higher in infertile cases (71.4%) compared to fertile controls (58.3%) [p value=0.30]. Vitamin D deficiency and infertility were positively correlated with the odd's ratio of vitamin D deficiency in infertile group as 1.91 (95% CI- 0.74-4.94). The p-value was >0.05, thus this correlation was not statistically significant. The mean vitamin D levels in infertile patients with endometriosis was higher and in PCOS, fibroid uterus and unexplained infertility was lower than mean vitamin D levels in fertile controls. Pearson's correlation coefficient calculation in the infertile cases showed no significant association of Vitamin D with TSH, FSH, LH and Prolactin (p value >0.05). **CONCLUSION:** Vitamin D seems to have a supportive role in female reproduction, however modest in nature. Further large-scale studies need to be done to decide whether vitamin D should be regularly supplemented in women seeking infertility treatment.

KEYWORDS : Vitamin D Deficiency, Infertility, Female Reproduction.

INTRODUCTION

Vitamin D receptors (VDR) have been discovered on female reproductive tissues such as ovarian granulosa cells, endometrium, placenta and the pituitary [1,2,3] and have inspired many researchers to study role of vitamin D in female reproduction. Vitamin D has shown to stimulate progesterone, estradiol and estrone production in human ovarian tissue [2]. It has been found that vitamin D modulates AMH, FSH and progesterone levels, thus possibly aiding in ovarian follicular development and luteinization [4]. Vitamin D also has been demonstrated to promote calcium transport in placenta [5,6] and regulate HOXA10 expression in human endometrial cells which is essential for endometrial development and uterine receptivity to implantation. [7,8]

Infertility is a complex disorder that affects 10 to 15% of couples [9] and has substantial medical, psychological, social and economic facets [10] thus requiring a comprehensive approach for evaluation and treatment.

The association of vitamin D deficiency and female infertility has been studied by many authors. The results of various studies have conflicting results on the extent to which vitamin D levels affects fertility in women and whether vitamin D levels should be routinely screened, and vitamin D regularly supplemented in infertile women as a part of infertility treatment.

MATERIALS AND METHODS

The study was conducted in the Department of Obstetrics and Gynaecology at Kasturba Hospital, Delhi during a period of 12 months (January–December 2019) after ethical clearance from the institutional ethical committee. The study subjects were recruited from patients attending Gynaecology OPD of Kasturba Hospital.

120 women of age 18-40 years, including 60 women with complaints of primary or secondary infertility as cases and 60 fertile women with at least one child presenting with complaints other infertility as controls were recruited for the study after written informed consent. All women were cohabiting with husband for more than one year.

Women with the following criteria were excluded from the study: (1) male factor infertility(2) infertility due to tubal factors, (3) patients having congenital anomaly of urogenital tract, (4) patients having history of liver/renal disease, osteoporosis, and rheumatoid arthritis, (5) history of antitubercular treatment ,antiepileptic treatment , steroid drug or OCP use in the last 6 months, (6) patients having history of smoking or alcohol abuse.

Fasting blood samples between Day 2 to 3 of menstrual cycle were taken from infertile women (n=60) and analysed for LH, FSH, Prolactin, TSH and Vitamin D levels. Along with this all relevant investigations for infertility were done in these infertile cases.

Fasting blood samples of age matched controls (n=60) were withdrawn and analysed for vitamin D levels.

Vitamin D levels were estimated using chemiluminescence

based immunoassay. Diagnosis of Vitamin D deficiency was made based on guidelines by The US Endocrine society.

- Vitamin D deficiency is defined as a level of ≤20 ng/ml.
- Vitamin D inadequacy is defined as a level between 21 and 29 ng/ml.
- Vitamin D levels ≥30 ng/ml are considered as adequate.

The percentage of vitamin D deficiency was determined in the whole study population as well as individually in both the groups of cases and controls. The percentage of vitamin D deficiency was compared in cases and controls. A p-value less than 0.05 was considered significant for difference in vitamin D deficiency in both groups. Mean vitamin D levels in infertile group and fertile group were determined and compared. A p-value less than 0.05 was considered significant for difference in mean vitamin D levels in both groups. Thus, the odd's ratio of infertile group for vitamin D deficiency was calculated and results were obtained.

Vitamin D levels in various underlying causes of infertility were compared with vitamin D levels in fertile controls.

Vitamin D levels in infertile cases were correlated with their endocrinal parameters (TSH, FSH, LH and prolactin levels) using Pearson's coefficient taking p value < 0.05 as significant.

Statistical Evaluation

The collected data was transformed into variables, coded and entered in Microsoft Excel. Data was analysed and statistically evaluated using SPSS-PC-19 version. Quantitative data was expressed in mean±standard deviation or median with interquartile range and difference between two comparable groups were tested by student's t-test (unpaired) or Mann Whitney 'U' test while for more than two graphs comparison ANOVA test or Kruskal Wallis H test was used followed by post-hoc test. Qualitative data were expressed in percentage and statistical differences between the proportions were tested by chi square test or Fisher's exact test. Spearman correlation coefficient (r<0.4 weak correlation; r =0.40-0.59 moderate correlation; r ≥0.60 strong correlation) was used to see the correlation between two quantitative variables. 'P' value less than 0.05 was considered statistically significant.

RESULTS

In our study, the mean age in infertile group was 27.37±4.29 years and in fertile group was 27.35±4.25 (p value=0.98). Among the 60 infertile cases, most of the patients i.e., 42 (70%) had primary infertility and only 18 (30%) had secondary infertility. The duration of infertility was 1-5 years in maximum number i.e., 45 (75%) patients, 6-10 years in 11 (18.3%) patients and more than 10 years in only 4 (6.7%) patients.

Among the 60 infertile patients in study group, 9 (15%) had endometriosis, 9 (15%) had fibroid uterus, 15 (25%) had PCOD, 2 (3.3%) had endometrial polyp, 3 (5%) had premature ovarian failure, 4 (6.7%) had hypothyroidism, 2 (3.3%) had hyperprolactinemia and 1 patient (1.7%) had both hypothyroidism and hyperprolactinemia as the underlying causes of infertility. In 15 patients out of total 60 (25%) infertile patients no apparent cause of infertility could be determined with basic infertility investigations; hence they were labelled as unexplained infertility.

I. VITAMIN D STATUS IN TOTAL STUDY POPULATION AND COMPARISION OF VITAMIN D STATUS IN INFERTILE AND FERTILE GROUP

In the present study consisting of total 120 patients (60 infertile cases and 60 fertile controls) ,78 out of 120 i.e., 65% patients had vitamin D deficiency. 19 out of 120 i.e., 15.8% patients had vitamin D insufficiency. 23 out of 120 i.e., 19.2% patients had sufficient vitamin D levels.

Table 1A : Vitamin-D status in infertile and fertile group

Vitamin D level	Infertile group (n=60)		Fertile group (n=60)		P value
	No.	%	No.	%	
Deficient (<20 ng/mL)	43	71.7	35	58.3	0.30
Insufficient (21-29 ng/mL)	8	13.3	11	18.3	
Sufficient (>30 ng/ml)	9	15.0	14	23.3	

Table 1B: Comparison of vitamin D levels between infertile and fertile group

	Infertile group (n=60)	Fertile group (n=60)	P value
Vitamin-D level (ng/mL) Mean +std. dev.	19.06±10.75	21.68±12.95	0.38
Vitamin-D level (ng/mL) Median (IQR)	16.57 (11.2-26.40)	17.15 (11.22-29.55)	

The odd's ratio for Vitamin D deficiency in infertile group was 1.91 (95% CI- 0.74-4.94). Since the odd's ratio was >1, vitamin D deficiency and infertility were positively correlated. However, since the p-value >0.05 the positive correlation was not statistically significant.

II. COMPARISION OF VITAMIN D LEVELS IN VARIOUS CAUSES OF INFERTILITY WITH FERTILE CONROLS

Table 2A: Comparison of vitamin D levels in underlying causes of infertility of infertile cases and fertile controls

A. INFERTILE CASES (n=60)		
Underlying causes of infertility	Vitamin D level (ng/ mL)	
	Mean value and Range	SD
Endometriosis (15%)	26.13 (7.80 - 42.40)	12.04
Fibroid uterus (15%)	16.21(8.90 - 42.53)	10.60
PCOD (25%)	16.85 (7.98 - 38.90)	7.82
Unexplained (25%)	19.48 (6.20 - 51.35)	13.10
Other causes (20%) (no. of individual cases < 8)	18.16 (7.50 - 34.80)	9.05
B. FERTILE CONTROLS (n=60)		
Fertile Controls	21.68 (6.20 – 56.90)	12.95

Table 2B: Comparison of vitamin D levels in various causes of infertility with fertile controls

	p value
Infertility d/t Endometriosis and Fertile Controls	0.22
Infertility d/t Fibroid uterus & Fertile Controls	0.18
Infertility d/t PCOD & Fertile Controls	0.36
Unexplained infertility & Fertile Controls	0.49
Other causes of infertility & Fertile Controls	0.56

III. CORRELATION OF TSH, FSH, LH AND PROLACTIN WITH VITAMIN D LEVELS IN INFERTILE WOMEN

Table 3: Correlation of hormonal profile in infertile patients with vitamin D level

	Vitamin D level	
	r value	p value
TSH	0.06	0.65
FSH	-0.16	0.20
LH	-0.06	0.63
Prolactin	-0.23	0.07

DISCUSSION

In our study we found that primary infertility was more common than secondary infertility. The duration of infertility was 1-5 years in maximum number i.e., 75% of patients. Among the 60 infertile patients in our study group, most common causes of infertility were found to be PCOD (25%), Endometriosis (15%) , Fibroid uterus (15%) and unexplained infertility (25%) (Table 2A). Other minor causes of infertility

were found to premature ovarian failure (5%), endometrial polyp (3.3%), anovulation due to hypothyroidism (6.7%), anovulation due to hyperprolactinemia (3.3%) and anovulation due to both hypothyroidism and hyperprolactinemia (1.7%).

Chiamchanya C et al (2008) [11], **Mittal et al** (2015) [12], **Deshpande et al** (2019) [13] and **Fernandes et al** (2020) [14] also found in their studies that primary infertility was more common than secondary infertility with majority of patients having duration of infertility less than 5 years. Endometriosis, PCOD and unexplained infertility were main causes of female infertility in these studies similar to our study. Endocrine causes of infertility like hypothyroidism and hyperprolactinemia were minor etiologic factors in causing infertility in women in these studies as well.

There was high percentage (65.0%) of women having vitamin D deficiency (25-hydroxy vitamin D < 20 ng/mL) in entire study population of 120 women who attended Gynaecology OPD at Kasturba hospital.

Vitamin D deficiency is quite common in Indian population with prevalence ranging from 40% to 99% in different populations [15,16,17]. Several causes lead to low levels of vitamin D in women coming to Kasturba hospital including burka practice and limited outdoor activities causing inadequate exposure to sunshine, improper diet and inadequate milk and dairy product consumption because of low socioeconomic status, low level of education and unspaced and unplanned pregnancies that cause nutritional deficiencies.

Vitamin D deficiency had a higher percentage in the infertile group (71.7%) compared to fertile group (58.3%) [Table1A]. However, the p-value was 0.30 making the difference between both groups statistically insignificant.

Both the mean and median level of vitamin D in infertile group was lower than mean and median level in fertile group [Table 1B]. However, the p-value was 0.38 making the difference between both groups statistically insignificant.

Vitamin D deficiency and female infertility were positively correlated with odd's ratio 1.91(95% CI- 0.74-4.94). However, since the p-value was >0.05, this positive correlation was not statistically significant.

Study by **Al-Jaroudi** et al (2015) [18] also found higher percentage of vitamin D deficiency in infertile women compared to fertile women ($p<0.01$). However, since pregnant women were taken as fertile controls in their study, haemodynamic changes of pregnancy and intake of calcium and vitamin D supplements in pregnancy could have been source of bias in the study.

Results of studies by **Jukic et al** (2019) [19] and **Fung et al** (2017) [20] demonstrated that reproductive age women with low vitamin D levels had lower chances of natural conception compared women with adequate vitamin D levels.

Tripathi et al (2017) [21] found significantly lower vitamin D levels in infertile women compared to fertile women and a positive association of vitamin D deficiency with female infertility which was statistically significant ($p<0.001$) in their study.

Somigliana et al (2016) [22], on other hand, found higher vitamin D levels in infertile women compared to fertile women, though statistically insignificant and concluded immaterial role of vitamin D in natural fertility.

The mean vitamin D level in patients having infertility due to endometriosis was higher (26.13±12.04 ng/mL) compared to fertile controls (21.68±12.95 ng/mL) with p=0.22 (Table 2A,2B). **Agic et al.** (2007) [23] and **Somigliana et al.** (2007) [24] also found higher vitamin D levels in patients of endometriosis compared to controls in their respective studies.

The mean vitamin D levels in patients having infertility due to PCOD (16.85±7.82 ng/mL), fibroid uterus (16.21±10.60 ng/mL) and unexplained infertility(19.48±13.10 ng/mL) were lower compared to fertile controls (21.68±12.95 ng/mL) with p-value= 0.36, 0.18 and 0.49 respectively (Table 2A,2B).

Davis et al (2019) [25] and **Krul-Poel et al** (2018) [26] found lower vitamin D levels among PCOD women compared to controls.
Paffoni et al. (2013) [27] and **Kumari et al** (2019) [28] found lower vitamin D levels in women having fibroid uterus compared to controls.

Al-Assadi et al (2018) [29] found higher vitamin D deficiency among women having anovulatory and unexplained infertility compared to fertile controls.

Among the study group of 60 infertile patients, Pearson's coefficient showed positive correlation of TSH levels with vitamin D levels and negative correlation of FSH, LH, prolactin levels with vitamin D levels (Table 3). However, the p-value was >0.05 in all these parameters, thus these correlations were statistically insignificant.

The results of **Pagliardini et al** (2015) [30] and **Tripathi S et al** [21] were also similar to our study in this respect where no significant correlation of Vitamin D levels found with TSH, LH, FSH and Prolactin levels in infertile women.

CONCLUSION

A higher percentage of vitamin D deficiency in infertile group compared to fertile group and a positive correlation of vitamin D deficiency and female infertility found in our study point to a supportive role of vitamin D in physiology of reproduction. However, the difference between both groups have been found to be statistically insignificant suggesting modest contribution of vitamin D in reproductive processes. Lack of significant correlation of hormonal levels of TSH, FSH, LH and prolactin to vitamin D levels point to the fact that vitamin D modulates female reproduction by mechanisms other than processes involving these hormones. Further large-scale studies need to be done to decide whether vitamin D should be regularly supplemented in women seeking infertility treatment.

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