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Study of Correlation of Serum Vitamin D Levels and Ovarian Reserve in Infertile Patients

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Abstract

The aim of the study is to assess any existing association between ovarian reserve and vitamin D levels. This study was designed to assess serum vitamin D levels and association with ovarian reserve in infertile patients. The mean age of cases was 34.3 whereas that of the controls was 33.3 years. There is association between age and ovarian reserve markers. As age advances AMH & AFC is decreased whereas FSH increases. In our study we found significant relation between age and ovarian markers. Present studies did not find any association with BMI. There was no correlation found between vitamin D and AMH. FSH, AFC levels in both the infertile and fertile women groups. In our study both groups showed vitamin D insufficiency and deficiency. The rate of vitamin D deficiency among women with impaired fertility is alarming. Taken altogether, our findings suggest that there is no association between 25 (0H) D and ovarian reserve markers.

Keywords: Vitamin D; Infertility; Anti Mullerian Hormone.

Introduction

Infertility is a burning problem affecting the psychological and social life, of not only the couple but also the family members. Infertility is defined as the inability of women to achieve conception after a year or more of regular, unprotected intercourse. The World Health Organization (WHO) estimates that approximately 8-10% of couples experience some form of infertility problems. Based on these estimates and on the current world population, 72.4 million women are currently infertile of these 40.5 million are currently seeking medical care [1]. Various factors (both male and female) are found to be responsible for infertility and its management puts substantial psychosocial demand on the couple, especially the female partner [2-4].

Considering modern trends of maternity postponement, one of the main causes for infertility in this situation is decreased ovarian reserve. The evaluation of functional ovarian reserve has arisen in an attempt to give better advice. Good ovarian reserve is necessary and the assessment of this will help in obtaining satisfactory results for successful conception.

Ovarian reserve is expressed in terms of the number of good quality oocytes that remain within the ovaries. As

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a woman's age increases, her ovarian reserve declines. It becomes mandatory to know the actual reproductive potential of the female evidenced by her ovarian reserve which includes Anti - Mullerian Hormone (AMH) levels and Antral Follicle Count (AFC). The AFC assessed by transvaginal ultrasonography provides direct visual assessment relating to the size and number of follicles that are any time responsive to FSH. AMH and Inhibin b are released products from the antral follicular pool. High FSH is an indirect marker, as it reflects a reduced feedback from the antral follicular pool as they become smaller in size.

Recent studies suggest that vitamin D may play a role in human reproduction. Vitamin D receptors (VDR) facilitate the biological activity of Vitamin D and are found in many cells throughout the body. VDR have been identified in reproductive tissues such as human testis, sperm, epididymis, seminal vesicle, prostate, ovaries, uterus, cervix, placenta, including breast, the pituitary, and hypothalamus [5-12]. Vitamin D deficiency has become a modern day epidemic, being the most common nutritional deficiency worldwide. In the United States at least 1/3rd of the population is vitamin D deficient (<20 ng/mL), with 41.7% of adults between the ages of 20-64 [13,14].

After a diagnostic infertility workup, 15-30% of couples will be found to have unexplained infertility [15]. One possibility for the unexplained infertility is vitamin D deficiency. This may be further supported by reports demonstrating the serum 1, 25-OH vitamin D levels correlating with AMH as seen in some knock out experiments.

We correlate vitamin D levels with ovarian reserve parameters like Follicle Stimulating Hormone (FSH), Anti Mullerian Hormone (AMH) and Antral Follicle Count (AFC) especially in infertile patients. Infertile women are recruited as study population and age matched non pregnant fertile women are taken as controls.

Materials and methods

Institutional ethical committee of Narayana medical college hospital, Nellore, Andhra Pradesh has approved the study with the following considerations:

This is a prospective study done in the Department of Obstetrics and Gynaecology, Narayana medical college & Hospital, Nellore for a period of 2 years (Oct 2015-Oct 2017). His study was designed to assess serum vitamin d levels in and its association with ovarian reserve parameters in infertile patients.

Women attending to gynecology outpatient department Narayana Medical College & Hospital, Nellore, NMCH, Nellore, AP with compliant of infertility.

200 subjects with 100 in each Group A & Group B. Group A: Infertile females. Group B: Fertile females.

*Inclusion Criteria***:** Infertile women in the age group of 25-45 years. With positive history of menstrual history (regular/irregular).

Exclusion Criteria: Presence of male factor infertility, presence of ovarian cysts (Benign/ malignant), History of previous ovarian surgeries (oophorectomy).

Anthropometric Measurements: Parameters such as height, weight & BMI were recorded. Weight was measured using a beam balance, to the nearest 0.1 kg and height to the nearest centimetre, using a tape stuck to the wall. BMI was calculated as the weight in kilograms divided by the square of height in meters.

Methodology: The determination of AMH, AFC & FSH is used for the assessment of the ovarian reserve in conjunction with other clinical and laboratory findings. Association of Vitamin d with ovarian reserve is observed in this study. *Antral follicle count:* Transvaginal ultrasound was performed during the early follicular phase (cycle day 2 or 3), by means of a transvaginal ultrasound scanner (Philips 11 *E), with a 5 MHz probe. In each ovary, the total number of small follicles (2-8 mm) was counted. The total follicle count was the sum of the follicle counts in each ovary. *AMH & FSH* are measured by chemiluminescent immunoassay. The Chemiluminescent Immunoassay kit is designed for the in vitro sensitive quantitative measurement of AMH inhuman serum, plasma, tissue homogenates, cell Iysates, cell culture supernates and other biological fluids. *Vitamin D* levels were measured in duplicate using a 2501-1 vitamin 0 total assay (DiaSorin, Stillwater, Minnesota, USA), using a competitive chemiluminescent immunoassay, as per the manufacturers guidelines.

Biochemical Analysis: Prepare all reagents, samples and standards; Add 5 µL standard or sample to each well and then add 50 IJ^{L} prepared Detection Reaqent Aimmediately. Shake and mix.

Incubate 1 hour at 37^{0}C; Aspirate and wash 3 times; Add 100 µL prepared Detection Reagent B. Incubate 30 minutes at 37^{0}C; Aspirate and wash 5 times; Add 100 µL Substrate Solution. Incubate 10 minutes at 37^{0}C. Read RLU value immediately. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Statistics: Frequency and percentage of each parameter was calculated and analysed. The data obtained was analyzed using SPSS software version 17.0 to generate graphs, tables etc.

Results

In the present study, age distribution of study & control population is shown maximum number in both groups belonging to 31-40 years, minimum in 41-45 years. The means of study & control are 34.3% and 33.3% respectively. BMI distribution in both study & control, only 33% of study population & 56% in the controls were with normal BMI whereas 44% of study populations are found to be overweight compared to only 17% in controls. Women in obese category sliqhtly differ in both groups (17 vs. 21). The mean BMI of study & control is 26 vs. 23.6.

The AMH levels are found to show inverse proportion between study & controls. 45% of study group were with low & very low fertility leveis of AMH compared to 16% in controls, 84% of controls were with optimal & satisfactory levels of AMH & the corresponding % in study group is 55. But in total, mean of study & controls are 2.4% vs. 4.4% showing an almost double in the controls. Normal AFC is seen in only 9% of study group compared to 15% of controls. 59% of study group is found to have low & very low count of AFC compared to only 26% of controls being with same counts. Themean of study vs. control is 5.9 VS. 8.3.

FSH levels are normal in 72% of study population compared to 86%in controls. High levels of FSH are seen 28% & 14% of study & controls with the means of 8.4 vs. 6.8. 55% of study population are with Vitamin D insufficiency & deficiency (42% vs. 13%) compared to 51% (42% vs: 9%) of controls. Almost normal levels of vitamin D seen in 45% & 49% of study & controls with mean 29.2 & 30.2 respectively.

AMH levels are showing negative correlation with age. As age advances AMH levers are decreasing.

AFC shows negative correlation with age. In age group of 36-45 yrs high of study population are seen with lower percentage of controls.

FSH levels are showing negative correlation with age. In the elderly age women (36-45 yrs) highernumber of women are seen in study compared to controls.

The correlation of vitamin D with age appears to be insignificant. Higher percentage of study population are seen in low and very low fertility levels of AMH compared to controls showing a negative correlation with BMI and with an insignificant P value. there was no correlation between BMI & AFC with insignificant P value.

Normal levels of FSH is seen in higher percent of controls with all grades of BMI, whereas it is the reverse with high levels of FSH.

No correlation is seen between vitamin D Levels & BMI among the study as well as controls.

The optimal and satisfactory levels of AMH are found to associate with normal vs. high, levels of FSH in 47% & 74% VS. 1 & 0 of study & controls respectively where as low & very low levels of AMH with normal vs. high FSH ranges seen in 16% & 2% vs. 36% & 14% of both groups.

In the study group with AMH in the optimal & satisfactory levels 31% are normal only and the rest in insufficiency and deficiency groups whereas with AMH in low and very low infertility only 14% are seen in normal vitamin D and the rest insufficiency and deficiency ranges. In the control group optimal & satisfactory levels of AMH, normal levels of Vitamin

Table 1: Correlation of Age with Vitamin D

Age (Yrs)	Vitamin – D Normal (>30 ng/dl)				Insufficency (20 – 30 ng/dl)				Deficiency (<20 ng/dl)			
	S	%	C	%	S	%	C	%	S	%	C	%
26-30	09	36	18	56.25	13	52	11	34.3	03	12	3	9.3
31-35	14	42.4	21	58.3	14	42.4	16	44.4	05	15.1	1	2.7
36-40	20	58.8	5	21.7	11	32.35	12	52.1	03	8.8	4	17.3
41-45	02	25	5	55.5	04	50	3	33.3	02	25	1	11.1

D seen is 39% the rest in other ranges with low and very low infertility vitamin D levels seen only 12%.

The optimal and satisfactory levels of AFC are found to associate with normal vs. high levels of FSH in 41% & 74% vs. 0 & 0 of study & controls respectively where as low & very low levels of AFC with normal vs. high FSH ranges seen in 31% & 12% vs. 28% & 14% of both groups.

The normal vitamin D association with normal & slightly reduced levels of AFC in 21% & 41% of study vs. controls, while the corresponding figures with low & poor AFC are 24% & 8%. The figures for vitamin D insufficiency in the same order of AFC are 18% vs. 26% &. 24% vs. 16%. The corresponding figures for vitamin D deficiency stand as 2% vs. 7% & 11% vs. 2%.

FSH within normal range 37% found to have normal Vitamin D levels where as with FSH high levels 8% being with normal vitamin D levels. The rest of people in the insufficiency & deficiency range in study group.

FSH within normal range 7% found to have normal Vitamin D levels where as with FSH high levels 2% being with normal vitamin D levels. The rest of people in the insufficiency & deficiency range in control group.

Table 2: Correlations of Age AND AFC

Age (Yrs)	Antral Follicle Count (AFC)															
	Normal count (>12 follicles)				Slightly reduced (8- 12 follicles)				Low count (4- 7 follicles)				Poor reserve (< 4 follicles)			
	S	%	C	%	S	%	C	%	S	%	C	%	S	%	C	%
26-30	5	20	5	15.6	10	40	25	78.1	6	24	2	6.25	4	16	0	00
31-35	4	15.1	8	22.2	10	30.3	22	61.1	13	39.3	6	16.6	6	18.1	2	6.25
36-40	2	5.88	2	8.69	10	29.4	9	39.1	8	23.5	3	13.0	14	41.1	7	30.4
41-45	0	00	0	00	0	00	3	33.3	1	12.5	0	00	7	87.5	6	66.6

Table 3: Correlation of BMI with Vitamin D

BMI (Kg/m2)	Vitamin - D											
	Normal (>30 ng/dl)				Insufficency (20 – 30 ng/dl)				Deficiency (<20 ng/dl)			
	S	%	C	%	S	%	C	%	S	%	C	%
≤ 18.5	4	80	2	33.3	1	20	4	66.6	0	00	0	00
18.5–24.9	18	39.1	31	55.3	12	26.0	20	35.7	16	34.7	5	8.92
25 – 29.9	20	45.4	8	42.1	18	40.9	10	52.6	6	13.6	1	5.26
≥ 30	5	33.3	8	42.1	9	60	8	42.1	1	6.66	3	15.7

Table 4: Correlation of BMI with AMH

BMI (Kg/m2)	Anti - Mullerian Hormone (AMH)															
	Optimal fertility (6.8 – 4.0 ng/dl)				Satisfactory (4.0 – 2.2 ng/dl)				Low Fertility (2.2 – 0.3 ng/dl)				Very Low Fertility (< 0.3 ng/dl)			
	S	%	C	%	S	%	C	%	S	%	C	%	S	%	C	%
≤ 18.5	1	20	4	66.6	2	40	1	16.6	0	00	1	16.6	2	40	0	00
18.5-24.9	5	13.8	30	53.5	18	50	16	28.5	8	22.2	9	16.0	5	13.8	1	1.7
25-29.9	11	25	11	57.8	16	36.3	5	26.3	14	31.8	3	15.7	3	6.81	0	00
≥ 30	3	20	12	63.1	5	26.3	6	31.5	4	26.6	1	5.2	3	20	0	00

Table 5: Correlations of BMI & FSH

BMI (Kg/m2)	Follicle Stimulating Hormone (FSH)							
	Normal value (1.4 –11 IU/ml)				High levels (11 – 15 IU/ml)			
	S	%	C	%	S	%	C	%
≤ 18.5	3	60	5	83.3	2	40	1	16.6
18.5–24.9	27	75	46	82.1	9	25	10	17.8
25 – 29.9	29	65.9	17	89.4	15	34.0	2	10.5
≥ 30	12	80	18	94.7	3	20	1	5.2

Discussion

This is a prospective study done in the Department of Obstetrics and Gynecology, Narayana, medical college & Hospital, Nellore. Our aim is to correlate serum vitamin' D levels with ovarian reserve parameters like FSH, AMH and AFC in Infertile patients in comparison with age matched controls. Prevalence of infertility ranges between 3.5-16.7% in developed countries and 6.9-9.3% in developing countries. It is estimated that overall median prevalence of Infertility is 9% worldwide rise of the mean. Many women in developed countries delay childbearing to fulfill their personal commitments. Increasing female educational levels and participation in the labour force has resulted in a clear age at which women deliver their first Child. Woman's fertility is remarkably reduced with increasing age. Many women will be faced with unexpected problems in becoming pregnant owing to decreased ovarian reserve.

Decrease in fertility with increases age is probably due to a decreasing number of primordial follicles after birth. Block observed that >250 000 primordial follicles were present at menarche, whereas only a few thousands or hundreds remain at the end of reproductive life [16]. The cyclic development of follicles is finely controlled by a sequence of hypothalamic pituitary ovarian interactions, and angiogenesis is an important component of both the follicular and luteal phase of an ovarian cycle [17]. Early follicular phase FSH level is increased with advancing age by a reduced inhibin mediated feedback towards the pituitary gland. The age related female infertility is mainly based on changes in ovarian reserve. Ovarian reserve can be defined as the number and quality of the remaining follicles and oocytes in both ovaries at a given age. Decline in follicle numbers dictates the occurrence of Irregular cycles and menopause, while quality decay of the oocytes results in decreasing fertility, defined as the capacity to conceive and give birth to a child.

As a result of diminished ovarian reserve, the women's ability to conceive naturally will limit. It has been shown that the rate of the ovarian reserve decline varies considerably between individual women, making it a challenge to design tests that estimate an individual's remaining reproductive lifespan at a given age. Good ovarian reserve is necessary for successful conception. An accurate assessment of reproductive age would be of help in counselling these women about their fertility potential and perhaps in scheduling pregnancies.

To date, there are in vivo, and in vitro data demonstrating that there might be a reidtionship between vitamin D deficiency and ovarian physiology in both animals there has been an increasing recognition that vitamin D plays an important role in female reproduction. For example, during pregnancy, vitamin D deficiency has been related to increased risks of' gestational diabetes, recurrent pregnancy loss, preeclampsia, and small-for-gestational-age babies. The purpose of the present study is to report the dynamics and role of vitamin D on ovarian physiology with a focus on ovarian reserve markers.

Human fertility is known to decline with increasing age. The main reasons of infertility are ovarian factors which are closely associated with the age of patients. There are studies addressing the effects of age on these markers in women with proven fertility.

AMH reflects the number of early and developing antral follicles. Van Rooij et al. (2005) reported that serum AMH levels decline with age in normal women with proven fertility [18]. They added that serum AMH represents the best endocrine marker to assess the age-related decline of reproductive capacity. A recent study has also concluded that AMH is able to specify a woman's reproductive age more realistically than chronological age alone.

As per the study of Banu Bozkurt et al., the AMH levels in both Study & controls showing a decline with a range of 3.1 to 0.8 & 3.4 to 0.6 respectively [19]. Present study also showing the same trend 3.08 to 0.84 vs 4.9 to 2.17.

Even in the study of Ludmila et al., which does not have controls the AMH levels are showing a downward trend ranging between 2.5 to 0.46. Above all studies including present study are showing significant P value [20].

It was recently demonstrated that pregnancy rates in women aged <35 years with levated basal FSH were higher than those of older women with normal levels of the hormone, reinforcing age as a main ovarian reserve marker.

FSH is easily accessible and a low-cost marker and that could be useful in pretreatment evaluation of specific groups of infertile women, such as those carrying an ovulatory cycles. Endometriosis or in patients over 35 years of age.

The present study is also showing the same trend indicating that with advanced age the FSH levels decrease showing a negative correlation.

The follicle growth pattern in the menstrual cycles in women of reproductive age has been

demonstrated by the ultrasonogram. At each cycle, several follicles are recruited, and grow at a rate of 2-6 mm daily in women in mid reproductive life (22-34 years); ovulation occurs at a mean follicular diameter of 16-27 mm. The antral follicular count i.e. the total number of follicles between 2-10 mm in diameter in the iwc ovaries is a parameter which has been used as a reflection o f reproductive age. There are no studies available in the literature about the correlation between age and vitamin D in the present study an attempt is made to find out the correlation between the two but in vain. There is no significant correlation between vitamin D and Age.

The decrease in rates of fertility in obese women arises from the negative interactions on follicular development or poor endometrial receptivity, rather than follicular reserve. In other words, AMH should better be considered as a good marker of ovarian reserve rather than a marker of fertility prediction. It is not possible explain the relationship between BMI and reproductive function with AMH levels. The present study doesn't seem to have any correlation between BMI & FSH. There are mechanisms beyond obesity that might explain the association of vitamin D deficiency with insulin resistance. First of all vitamin D may have a beneficial effect on insulin action by stimulating the expression of insulin receptor and thereby enhancing insulin responsiveness for glucose transport The vitamin D responsive element is found in the promoter of the human insulin gene and transcription of the Human insulin gene is activated by 25 (OH)-D 3. Secondly, vitamin D regulates extracellular and intracellular calcium which is essential for insulin mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue. A negative correlation was found between BMI value and vitamin D levels in both fertile and infertile women. There is evidence that low vitamin D levels are associated with obesity and vice-versa. Low vitamin D intake might be an independent predictor of obesity.

Studies also suggest that higher levels of FSH results infertility.

In the present study also it was proved that infertile population (study group) is having a higher range of FSH compared to fertile group (controls).

AFC has been shown to be an excellent predictor of ovarian reserve and espouse, with significant superiority in relation to other markers. Studies also demonstrated significant correlations between AFC and commonly performed serum ovarian reserve tests and between AFC and AMH in the serum. Circulating Vitamin D and AMH levels suggest a novel relationship between this vitamin and a clinically useful marker of ovarian reserve. Thus, assessment of vitamin D status theoretically might be considered as part of the routine workup in infertile women. Additionally, appropriate supplementation of patients with vitamin D deficiency might translate to better ovarian reserve markers and better ovarian follicular dynamics.

The existing literature does not provide any definitive and consistent pattern for how vitamin D may affect AMH production. The key finding in our prospective study in, women of child bearing age that serum vitamin D levels appear to be unrelated to AMH levels. Merhi et al. had also reported no relationship between serum vitamin D and AMH levels in women aged 35 to 40 years [21]. There is no consensus that how vitamin D affects AMH production. Therefore, the age of a woman and/or ovarian status would not be expected influence the effect of 25 (OH) D on the production of AMH. Consistent with this, the inclusion of age in the regression analysis did not diminish the relationship between 25 (OH) D and AMH and may even have slightly strengthened it. The existing literature does not provide any definitive and consistent data pattern regarding influence of vitamin D on AMH production.

In present study the levels of vitamin D & AMH shows a positive correlation both in study and control population the sample size being small it is difficult to arrive a reasonable conclusions.

Conclusion

Infertility being the burning problem globally effecting 9% of people standing as a social stigma for the effected couples. Continuous advanced research attempts to find out the relevant investigations and best treatment for these problems are still going on. This study mainly intends to find out the correlation of vitamin D with ovarian reserve markers in infertile females. In this study, there exits an inverse relationship between age and AMH (along with AFC). Positive correlation exists between age & FSH irrespective of fertility status. Vitamin D does not seem to have any significant correlation with ovarian reserve markers.

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