Original Article

Role of Vitamin D Deficiency in Female Infertility and ART Outcomes

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Abstract

Objective: To assess the role of vitamin D deficiency and perceive the outcomes of ART among vitamin D deficient females in infertile females attending infertility clinic in Riyadh Saudi Arabia.

Place and Duration: A retrospective cohort study of all vitamin D deficient infertile women who presented to Reproductive endocrinology and infertility department (REIMD), King Fahd Medical City infertility center from January 2012 and January 2016 for a period of 4 years was performed.

Methodology: Random sampling was done to take around 192 infertile females who fulfill the inclusion criteria for the study. The association of vitamin D deficiency in infertile females between deficient and insufficient groups was distinguished followed by analysis of the outcome (aborted, ectopic pregnancy, molar pregnancy, no pregnancy, successful pregnancy and unknown) after the intervention done in the form of different ART options (OI, IUI, IVF, ICSI).

Results: Among 192 patients in total, 56.2% had primary infertility,36.5% had an irregular menstrual cycle,33.3% had PCOS, 78.1% underwent IVF, and successful pregnancy was observed in only 15.1%. Of the included women, 88.5% were vitamin D deficient, (less than 50nmol/l) and 5.2% were vitamin D insufficient(50-75nmol/l). In infertile women with low vitamin D, there was also decrease in the level of FSH and LH. When vitamin D deficient (<50nmol/l) and vitamin D insufficient groups(50-75nmol/l) were compared the maximum duration of infertility among vitamin D deficient (29.4%), and vitamin D insufficient (40%) was six years. Though vitamin D deficient patients had primary infertility (57.6%), Vitamin D insufficient patients had secondary infertility (50%).Almost 37.6% of vitamin D deficient and 30% of vitamin D insufficient groups had an irregular menstrual cycle. Most common ultrasound manifestation in vitamin D deficient (33.5%) and vitamin D insufficient cases (40%) was PCOS. 80.6% of vitamin D deficient patients underwent IVF compared to 40% of vitamin D insufficient patients with statistical significance less than 0.05(p value=0.008). Pregnancy with IVF was observed in 21.8% of vitamin D deficient and 10% of vitamin D insufficient patients with statistical significance less than 0.05(p value=0.009). As for the outcome, no pregnancy was observed in 62.3% vitamin D deficient and 40% of vitamin D insufficient patients. Successful pregnancy was confirmed in 15.3% of vitamin D deficient and 20% in vitamin D insufficient cases.

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Conclusion: Both vitamin D deficiency, as well as insufficiency, adversely affect the outcome of ART contributing to lower pregnancy rates among Arabian women in the reproductive age group. Vitamin D supplementation might bring on treatment success in infertile patients undergoing IVF and is recommended for infertile women in our region.

Key words: Infertility, IVF, Vitamin D deficiency, Vitamin D insufficiency, ART.

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Introduction

Infertility is "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse".[1] Infertility is estimated to be between 12-14%, and vitamin D deficiency is one of the contributory factors for infertility.[2] Although the role of Vitamin D in infertility is uncertain, it is still in the scope of research in many fields of medicine. The deficiency of vitamin D defined as the concentration of 25-hydroxycalciferol <20 ng/ml or 50 nmol/l that is frequently noted in patients attending infertility clinics. Vitamin D level in serum is determined by measuring levels of serum 25-hydroxyvitamin D 25(OH) D concentration. Vitamin D deficiency is labeled when 25(OH) D levels are less than 50 nmol/L (20 ng/mL) whereas vitamin D insufficiency is declared at level 50 to 75 nmol/L (20-30 ng/mL).[3] It is accepted that vitamin D treatment is required for patients with a concentration below 20 ng/ml (up to 50 nmol/l), especially in obese women, those with insulin resistance and small ovarian reserve, and in men with oligo- and asthenozoospermia.[3,4]

Vitamin D has a direct effect on AMH production, and thus increases longer maintenance of ovarian reserve in patients with its higher concentration.[3] Serum vitamin D concentration in healthy women is higher compared to women with PCOS who present more often with obesity, insulin resistance, hyperandrogenemia and amenorrhea.[4] The supplementation with vitamin D should be applied in the schemes of PCOS treatment both due to improved insulin resistance and the results of infertility treatment.[5] Rudick et al. 2012, observed that the clinical pregnancy rate progressively decreases with declining vitamin D status in non-Hispanic whites, but not in women of Asian ethnicity.[7,8] According to B. Rudick et al., 2012, the relationship between vitamin D status and pregnancy rates differed by race (P, 0.01). So, the race is a significant factor to determine the role of Vitamin D deficiency in ART outcomes.[2,6] Previous studies have shown a significant decline in clinical pregnancy rate among recipients of egg donation of different ethnicities who were vitamin D deficient. Vitamin D deficiency results in significantly lower pregnancy rates in women undergoing single blastocyst transfer.[7]

Both Ozkan and Rudick have demonstrated the importance of ethnic factor in the association of vitamin D deficiency and infertility.[6,8] Research is needed to elucidate further the mechanism by which vitamin D acts, the ethnic heterogeneity in vitamin D metabolism and its subsequent effects on IVF success.[2, 6] As data is not available from our region, and race/ ethnicity is an important factor that influences the role of vitamin D in ART outcomes, it was considered important to conduct this research.

The physiological importance of vitamin D is related to calcium homeostasis and skeletal growth. Its deficiency is also associated with metabolic disorders in the form of diabetes and obesity, cardiovascular diseases and cancers, autoimmune and infectious diseases psychological disorders such as depression and chronic pain.[11, 12] It is related with the polycystic ovarian syndrome, insulin resistance, metabolic syndrome, in vitro fertilization IVF failure and, endometriosis.[3,13] Ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, and hyperandrogenism also occur due to Vitamin D deficiency.[12]

Vitamin D deficiency has been proven to affect fertility in mammals, but data in human is less convincing. In particular, data on in vitro fertilization (IVF), are sparse and conflicting.[11,12] Lerchbaum E, 2012 has described the importance of vitamin D role in female fertility. Although Vitamin D receptors are present in pituitary its receptors on female reproductive organs like ovaries and endometrium

predate its role in female infertility.[13,14] Vitamin D deficiency is accompanied by calcium dysregulation, which contributes to the development of follicular arrest in women with PCOS and results in menstrual and fertility dysfunction. Vitamin D might influence steroidogenesis of sex hormones thus affecting estradiol and progesterone levels in healthy women and high 25(OH)D levels might be associated with endometriosis. [14]

Role of Vitamin D deficiency in females with PCO is also modulated by effects on gene transcription. There is reported relationship of vitamin D deficiency within fertile females who are PCO and exhibit metabolic disorder.[15] Vitamin D deficiency is associated with female infertility and adverse IVF outcomes, and there is a need for studies to determine the therapeutic benefits of vitamin D supplementation.[16] Even if vitamin D deficient infertile females get pregnant by intervention like IVF, they are exposed to increase maternal and neonatal adverse outcomes.[16,17] Significant differences as a response on ovulation stimulation, number and quality of embryos depending on vitamin D concentration were not observed in none of the analyzed papers concerning the role of vitamin D in vitro fertilization (IVF). [18]

Also, in previous studies, different criteria for clinical pregnancy has been taken. According to Ozkan et al., Clinical pregnancy (CP), is defined as evidence of intrauterine gestation sac on ultrasound, following IVF.[17] Whereas the FDA approved definition, include evidence of pregnancy by clinical (fetal heartbeat) or ultrasound parameters (ultrasound visualization of a gestational sac, an embryonic pole with a heartbeat). It includes ectopic pregnancy and multiple gestational. Both previous studies have taken different parameters for clinical pregnancy. In our study clinical pregnancy is defined according to FDA standardization. In previous studies, infertility is discussed as general with mechanism and effect of decreased Vitamin D on ovarian function and clinical pregnancy rate. Like, Pludowski P et al. 2013, in his study has taken infertility as a general spectrum while we aimed to focus on the treatment of infertility in the form of ART which includes ovulation induction (OI), Intrauterine insemination (IUI) and in vitro fertilization (IVF).[10,19] The outcomes that are considered include in the form of clinical and biochemical pregnancy, miscarriage, ectopic and successful pregnancy resulting in live birth.

The prevalence of vitamin D deficiency in Saudi Arabia is 35%. In spite of adequate sunlight exposure 90% cases are due to dietary insufficiency. Vitamin D is an emerging factor influencing female fertility and IVF outcome. Hence additional studies are pressingly needed to confirm a causal relationship and to investigate the potential therapeutic benefits of vitamin D supplementation. [20]

Methodology

A retrospective cohort study of infertile women who were having low vitamin D level and presented to King Fahd Medical City infertility center from January 2012 and January 2016 for 4 years was performed. Random sampling was done to take 192 infertile females attending Reproductive endocrinology and infertility department for the study. Association between vitamin D deficient (less than 50nmol/l) and insufficient group (50-75nmol/l) through the application of chi-square test was evaluated to see the relationship between serum OH Vit D3 and major outcome measure (successful pregnancy). IRB approval was taken from the institutional review board of King Fahad Medical City. (15-452).

All infertile females who were vitamin D deficient or insufficient were pooled, and then ART outcomes were analyzed.

Initially, the sample size was calculated to be 192 using the standard equation, depending on the categorical data, with prevalence %. Bound of error is taken 5% with 95% confidence interval. As the data is categorical, the following formula for sample size calculation was applied $n = z2 * \frac{p(1-p)}{d2}$

The calculated sample size comes to 192 with 20% wastage.

Inclusion criteria:

1. A complete record of the patients and laboratory investigation.
2. Saudi female
3. Age 17-38
4. BMI 18–25 kg/m2
5. Undergoing IVF

6. Vitamin D deficiency less than 50 nmol/L (20 ng/mL) and vitamin D insufficiency level 50 to 75 nmol/L

Exclusion criteria:

1. Incomplete files
2. Infertile female with normal Vitamin D level

Data collection procedure: The investigation results were collected from the electronic data record system. Data collection tool: clinical and laboratory findings were compiled on excel sheet.

After complete collection, data was entered on SPSS version 20. Frequencies and percentages were taken as categorical variables. Association between vitamin D deficient and insufficient group through the application of chi-square was evaluated to see the relationship between Vitamin D and major outcome measure (successful pregnancy). A p-value less than 0.05 was be taken as significant.

Results

Among 192 patients in total, 56.2% had primary infertility,36.5% had an irregular menstrual cycle, 33.3% had PCOS, 78.1% underwent IVF, and successful pregnancy was observed in only 15.1%. Of the included women, 88.5% were vitamin D deficient (less than 50nmol/l), and 5.2% were vitamin D insufficient(50-75nmol/l). (Table I)

Mean, and standard deviation of lab investigations of hormones and vitamin D level are depicted in table II. In infertile women with low vitamin D, there was also decrease in the level of FSH and LH.

In table III, when vitamin D deficient (<50nmol/l) and vitamin D insufficient groups(50-75nmol/l) were compared the maximum duration of infertility among vitamin D deficient (29.4%) and vitamin D insufficient (40%) was six years. Though vitamin D deficient patients had primary infertility (57.6%), Vitamin D insufficient patients had secondary infertility (50%). Almost 37.6% of vitamin D deficient and 30% of vitamin D insufficient groups had an irregular menstrual cycle. Most common ultrasound manifestation in vitamin D deficient (33.5%) and vitamin D insufficient cases (40%) was PCOS. 80.6%Of vitamin D deficient patients underwent IVF compared to 40% of vitamin D insufficient patients with statistical significance less than 0.05(p value=0.008). Pregnancy with IVF was observed in 21.8% of vitamin D deficient and 10% of vitamin D insufficient patients with statistical significance less

Table I: Clinical characteristics of patients n=192

Characteristics	Categories	N=192 (n%)
Age	< 25	23(12.0%)
	25-35	128(66.6%)
	>35	41(21.4%)
Duration of infertility	1-2 years	26(13.5%)
	3-4 years	62(32.3%)
	5-6 years	46(24%)
	>6 years	58(30.2%)
Type of infertility	Primary infertility	108(56.2%)
	Secondary infertility	84(43.8%)
Cause of infertility	Endometriosis	4(2.1%)
	Male and female factor	12(6.3%)
	Male factor	31(16.1%)
	PCO	64(33.3%)
	Tubal	15(7.8%)
	Unexplained	65(33.9%)
	Uterine	1(0.5%)
Menstrual cycle	Irregular	70(36.5%)
	Oligomenorrhoea	2(1%)
	Regular	120(62.5%)
Ultrasonography	Endometriosis	4(2.1%)
	Normal	99(51.6%)
	Ovarian cyst	5(2.6%0
	PCO	73(38%)
	Uterine (anomaly, fibroid)	11(5.7%)
Vitamin D level	Deficient (Less than 50nmol/l)	170(88.5%)
	Insufficient (50-75nmol/l)	10(5.2%)
	Missing	12(6.3%)
Intervention	IVF	150(78.1%)
	Oral/injectables/IUI	14(7.3%)
	Unknown	28(14.6%)
Response	No pregnancy	117(60.9%)
	Pregnancy with IVF	43(22.4%)
	Pregnancy with oral injectables	1(0.5%) 6(3.1%)
	Spontaneous pregnancy	
	Unknown	25(13%)
Outcome	Aborted	9(4.7%)
	Ectopic pregnancy	3(1.6%)
	Molar pregnancy	1(0.5%)
	No pregnancy	115(59.9%)
	Successful pregnancy	29(15.1%)
	Unknown	35(18.2%)

Table II: Lab investigations of patients (n=192)

Serum levels	Minimum	Maximum	Mean/St Dev
FSH	0.35	31.08	6.2 ± 3.4
LH	0.10	150.7	9 ± 11.8
VITAMIN D	<0.1	73.12	23.9 ± 13.2

Table III: Association between vitamin D and infertility and Lab investigations of patients (n=180) valid cases out of total 192 patients.

Variables	Vit D <50nmol/l (vitamin D deficient) N=170	Vit D (50-75) nmol/l (vitamin D insufficient) N=10	P value
Age			
< 25	21(12.4%)	0%	
25-35	112(65.8%)	9(90.0%)	**0.401**
>35	37(21.8%)	1(10%)	
Duration of infertility			
1-2 years	25(14.7%)	1(10%)	
3-4 years	53(31.2%)	4(40%)	**0.735**
5-6 years	42(24.7%)	1(10%)	
>6 years	50(29.4%)	4(40%)	
Type of infertility			
Primary	98(57.6%)	5(50%)	**0.746**
Secondary	72(42.4%)	5(50%)	
Cause of infertility			
Tubal	15(8.8%)	0(0%)	**0.343**
Male and female factor	9(5.3%)	2(20%)	
Male factor	21(12.3%)	2(20%)	
PCO	57(33.5%)	4(40%)	
Endometriosis	4(2.4%)	0(0%)	
Unexplained	63(37.1%)	2(20%)	
uterine	1(.6%)	0(0%)	
Menstrual cycle			
Irregular	64(37.6%)	3(30%)	**0.772**
Oligomenorrhoea	2(1.2%)	0(0%)	
Regular	104(61.2%)	7(70%)	
Ultrasonography			
Endometriosis	4(2.4%)	0(0%)	**0.913**
Normal	90(52.9%)	5(50%)	
Ovarian cyst	5(2.9%)	0(0%)	
PCO	62(36.5%)	5(50%)	
Uterine (anomaly, fibroid)	9(5.3%)	0(0%)	
Intervention			
IVF	137(80.6%)	4(40%)	**0.008***
Oral/injectables/IUI	11(6.5%)	3(30%)	
Unknown	22(12.9%)	3(30%)	
Response			
No pregnancy	108(63.5%)	4(40%)	**0.009***
Pregnancy with IVF	37(21.8%)	1(10%)	
Pregnancy with oral Injectable	0%	1(10%)	
Spontaneous pregnancy	6(3.5%)	0(0%)	
Unknown	19(11.2%)	4(40%)	
Outcome			
Aborted	9(5.3%)	0(0%)	
Ectopic pregnancy	1(.6%)	0(0%)	**0.289**
Molar pregnancy	1(.6%)	0(0%)	
No pregnancy	106(62.3%)	4(40%)	
Successful pregnancy	26(15.3%)	2(20%)	
Unknown	27(15.9%)	5(40%)	

**P<0.05 was taken as the level of significance*

than 0.05(p value=0.009). As for the outcome, no pregnancy was observed in 62.3% vitamin D deficient and 40% of vitamin D insufficient patients. Successful pregnancy was confirmed in 15.3% of vitamin D deficient and 20% in vitamin D insufficient cases.

Discussion

IVF outcomes associated with Vitamin D deficiency (level < 10 ng/ml) is an independent predictive parameter for IVF success.[1] In our study, 82.1%Of vitamin D deficient patients underwent IVF compared to 36.4% of vitamin D insufficient patients with statistical significance less than 0.05 (p value=0.001). Pregnancy with IVF was observed in

23.1% of vitamin D deficient and 9.1% of vitamin D insufficient patients with statistical significance less than 0.05(p value=0.003). Better results in patients without calciferol insufficiency are explained by reports about the high concentration of vitamin D and its metabolites in human in decidua collected in the 1st trimester of pregnancy which suggests its contribution in proper implantation and local immunological preference of the embryo.[2]

Rudick in his study of the 188 patients, reported that 21% (39/188) were vitamin D deficient (25(OH)D <20 ng/ml), 37% (70/188) were vitamin D insufficient (20–30 ng/ml) and only 42% (79/188) were vitamin D replete 25(OH)D >30 ng/ml).[5] In our study,87.8% had vitamin D deficiency (less than 50nmol/l), and 5.6% had Vitamin D insufficiency (50-75nmol/l). Vitamin D replete patients were not included in our study.

In a study conducted by Garabedian et al. in 2013,54.9% had insufficient 25(OH)D levels and 45.1% had sufficient levels.[17] Women with sufficient levels had significantly higher rates of clinical pregnancy per IVF cycle started (52.5%) compared with women with insufficient levels (34.7%; $p < 0.001$).[17] Implantation rates were also higher in the sufficient 25(OH)D group, but the results were not statistically significant. As for the outcome, in our study pregnancy was not observed in 61.8% vitamin D deficient and 36.4% of vitamin D insufficient patients. Successful pregnancy was confirmed in 15% of vitamin D deficient and 18.2% in vitamin D insufficient cases.

Recent retrospective study postulated that vitamin D deficiency might negatively affect pregnancy rates with an effect mediated through the endometrium, given that vitamin D deficiency was not correlated with ovarian stimulation characteristics or with markers of embryo quality. Vitamin D may exert an effect on IVF cycle outcomes via the endometrium by VDR that is expressed in the endometrium and plays a vital role in activating the innate immune response.[9] Both vitamin D deficiency, as well as insufficiency, adversely affect the outcome of IVF contributing to lower pregnancy rates among Arabian women in the reproductive age group. Vitamin D supplementation might bring on treatment success in infertile patients undergoing IVF and is recommended for infertile women in our region.

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Conclusion

Both vitamin D deficiency, as well as insufficiency, adversely affect the outcome of ART contributing to lower pregnancy rates in the reproductive age group. Vitamin D supplementation might bring on treatment success in infertile patients undergoing IVF and is recommended for infertile women.

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