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Impact of vitamin D deficiency on reproductive dysfunction in West Algeria women of reproductive age

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ABSTRACT

In addition to sex steroid hormones, vitamin D has a modulatory reproductive action due to the vitamin D receptor and vitamin D metabolizing enzymes that are found in human reproductive tissues. This study aimed to evaluate and explore the impact of vitamin D on female infertility. Authors conducted a prospective study of 394 infertile women from the region of Tiaret (western Algeria).

Authors study revealed a predominance of hypovitaminosis in 80.8% of all patients, with no significant relationship between vitamin D status and age. However, a significant association between residence, Body Mass Index and vitamin D was found (P<0.0001). The association of 25(OH)D and certain pathologies (Polycystic ovary syndrome, endometriosis, miscarriage and irregular menstrual cycle) was very significant (P<0.0001). Women with vitamin D deficiency were the most affected by uterine and ovarian abnormalities. An inverse correlation was highlighted between vitamin D and different hormones, infertility duration and supplementation. Moreover, women with long lasting infertility (55-96 months and over 96 months) were deficient in vitamin D (31.3% and 19.5%, respectively). In addition, miscarriages were more noted in vitamin D deficient women (96 cases, 36.6%); however, the majority of women with normal vitamin D status had no history of miscarriages (93.3%) P χ^2<0.0001.

Hypovitaminosis D is associated with long durations of infertility, high number of miscarriages, a significant prevalence of Polycystic ovary syndrome, irregular menstrual cycles. Thus, good control of vitamin D status is a necessity for improving female fertility.

INTRODUCTION

In literature, vitamin D is defined as a steroid hormone produced by the skin after sun exposure with a rate of 80% to 90%. A minor quantity of total body vitamin D, however, comes from food and dietary supplements [1]. Vitamin D deficiency is prevalent in females of childbearing age [2]. The main causes of this deficiency are obesity, lifestyle changes and reduced sun exposure [3]. Research demonstrates that, in addition to sex steroid hormones, vitamin D regulates reproductive actions. This is due to the presence of vitamin D receptor (VDR) and vitamin D metabolizing enzymes in human reproductive tissues [4]; including the ovary, uterus, placenta and pituitary, which links vitamin D to reproductive health [5].

The World Health Organization (WHO) has approximated that 48 million couples are affected by infertility, with a global estimated prevalence of 10-15% [6]; polycystic ovarian syndrome (PCOS) [7], obesity [8], endometriosis [9], are the main causes of female infertility.

Several studies have revealed correlations between these pathologies and vitamin D deficiency. However, those that considered all parameters related to female infertility with

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low vitamin D levels in west Algeria were very rare, so we conducted a prospective study on Algerian women of childbearing age to elucidate the role of vitamin D on female fertility and its impact on the most frequent conditions associated with impaired female fertility such as polycystic ovary syndrome (PCOS), endometriosis and regularization of the menstrual cycle.

MATERIALS AND METHODS

Study setting and period

Our survey was carried out at the level of the medically assisted procreation clinic in the region of Tiaret (Western Algeria, North Africa) along a period of one year from September 2021 to September 2022.

Study design

A prospective epidemiological study was performed in order to assess the relationship between vitamin D deficiency and impaired female fertility.

Sample size and sampling procedure

Our study was carried out on a sample of 394 infertile women. All patients with fertility disorders aged between 18 and 40 who agreed to participate in our study and gave their consent were included. Patients aged over 40 and those supplemented with vitamin D were excluded as were women under specific drugs effects inducing vitamin D deficiency such as corticosteroids and antiepileptic drugs.

Data collection tools and procedures

Studied parameters were: age, residence, weight status, 25 OH vitamin D levels, presence of certain pathologies (PCOS, endometriosis, uterine abnormalities, ovarian abnormalities, miscarriages), menstrual cycle regularity, hormonal profile (FSH, LH, estrogen, progesterone) and the consequences of vitamin D supplementation.

All participants were classified into 3 subgroups: Deficiency (serum 25OH-D <20 ng/ml), Insufficient (serum 25OH-D ≥20 to <30 ng/ml), and Normal (serum 25OH-D ≥30 ng/ml) **[10].**

Data analysis

The data collected during the survey were assessed using statistical software (SPSS Inc., Chicago, IL, USA) version 25, and the results were considered significant when $p<0.05$. To compare qualitative values, we used the chi-square test, while the quantitative values were expressed as mean ± standard deviation. Pearson's correlation and the one-way ANOVA test were applied for the comparative study.

Ethics

Considering Decree No. 387 (article 25) dated 31 July 2006 about ethical trials in Algeria, we obtained the required access authorizations to the concerned health facilities to accomplish our study protocol. The medical committee of the Tiaret region medically assisted procreation clinic and the biology department of Djillali Liabes University approved the study. Written consent was obtained.

RESULTS

Into our study, 394 infertile women were recruited. They had a mean age of 33.23±6.16 years. A low rate of 25-hydroxyvitamin D (deficiency) was mainly noted in 262 cases, (66.7%) and 56 cases had an insufficient level (14.2%); while only 75 cases (19.1%) had normal vitamin D levels. No significant relationship was found between Vitamin D status and age. A significant link between residence, BMI and vitamin D was, however, found in our series ($P\ \chi^2 <0.0001$). Most obese, overweight, and lean women had Vitamin D deficiency at 27.5%, 19.8% and 12.2%, respectively, while normal vitamin D levels were more noticeable in women with normal weight status at 84 %. Moreover, hypovitaminosis was more dominant in women from urban areas (210 cases), compared to 108 cases of rural women.

Pearson correlation revealed that the more that serum level indicates increase of 25-hydroxyvitamin D, the greater the decrease in duration of infertility ($P<0.0001$) (Figure 1A). Women with long durations of infertility (55-96 months and over 96 months) were deficient in vitamin D (31.3% and 19.5%, respectively) compared to the group with normal serum vitamin D levels (8% and 0%, respectively) (Table 1).

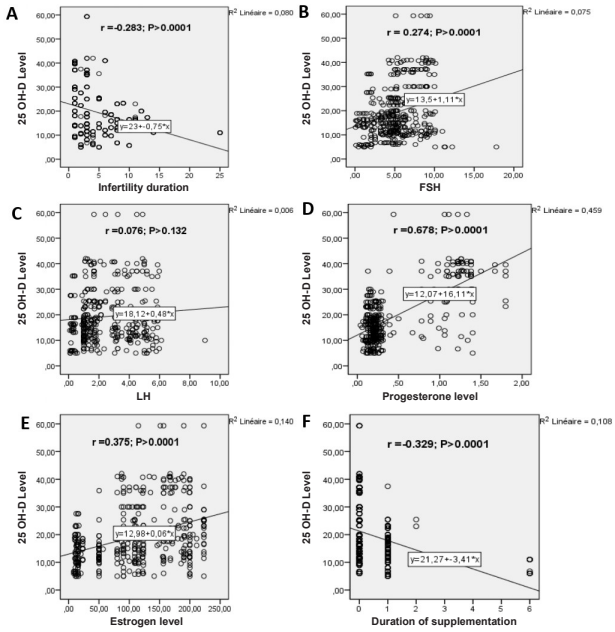

Figure 1. Linear correlation between vitamin D level and infertility duration, hormone profile, and duration of supplementation

Our study highlighted a significant prevalence of PCOS (26.21%), most were deficient in serum vitamin D level (87 cases), and the link between vitamin D deficiency and PCOS was significant $P\chi^2<0.000$. Besides PCOS, polycystic ovary was also more noted in vitamin D deficient patients (14 cases). Concerning endometriosis, our results did not demonstrate a relationship with vitamin D deficiency.

With regard to miscarriages, we found that the highest number of pregnancy losses occurred in the vitamin D deficient women group (36.6% for 1-3 miscarriages and 2.3% for 3-5 miscarriages), while most females with normal vitamin D status had no history of miscarriages (93.3%) $P\ \chi^2<0.0001$. Furthermore, the majority of Vitamin D

deficient patients group had irregular menstrual cycles (58.4%); whereas 84% of all women with normal vitamin D status had no cycle disorders.

Table 1. Relationship of vitamin D with age, Body Mass Index, area, and infertility duration

		Vitamin D status			P Value
		Deficiency	Insufficient	Normal	
Age (years)	Mean±SD	33.15±5.74	34.18±7.62	32.83±6.38	0.429
	21-30	108 (41.2%)	16 (28.6%)	34 (45.3%)	0.249
	31-40	108 (41.2%)	25 (44.6%)	26 (34.7%)	
	>40	46 (17.6%)	15 (28.6%)	15(20%)	
BMI (kg/m²)	Mean±SD	25.21±5.85	25.54±6.35	23.88±3.17	0.13
	<18,5	32 (12.2%)	10 (17.9%)	0 (0.0%)	<0.0001
	18,5-24,9	106 (40.5%)	16 (28.6%)	63 (84%)	
	25-29,9	52 (19.8%)	15 (26.8%)	11 (14.7%)	
	>= 30	72 (27.5%)	15 (26.8%)	1 (1.3%)	
Area	Urbain	170 (64.9%)	40 (71.4%)	30 (40%)	<0.0001
	Rural	92 (35.1%)	16 (28.6%)	45 (60%)	
Infertility duration (Months)	Mean±SD	5.81±4.39	4.57±3.68	2.29±1.44	<0.0001
	<=12	30 (11.5%)	15 (26.8%)	35 (46.7%)	<0.0001
	13-54	99 (37.8%)	15 (26.8%)	34 (45.3%)	
	55-96	82 (31.3%)	15 (26.8%)	6 (8%)	
	>96	51 (19.5%)	11 (19.6%)	0 (0.0%)	

The most affected category by uterine abnormalities was that of women who had vitamin D deficiency (40 cases of uterine fibroids, 10 cases of uterine malformation, and 5 cases of tubal obstruction). Statistical analysis revealed that the relationship between vitamin D and these pathologies was significant – as illustrated in Table 2.

Table 2. Relationship of vitamin D status with female pathologies

Pathologies		Vitamin D status			P Value
		Deficiency	Insufficient	Normal	
PCOS	No	175 (66.8%)	46 (82.1%)	69 (92%)	<0.0001
	Yes	87 (33.2%)	10 (17.9%)	6 (8%)	
Endometriosis	No	260 (99.2%)	53 (94.6%)	63 (84%)	<0.0001
	Yes	2 (0.8%)	3 (5.4%)	12 (16%)	
Miscarriage	1-3 miscarriages	96 (36.6%)	0 (0.0%)	5 (6.7%)	<0.0001
	3-5 miscarriages	6 (2.3%)	0 (0.0%)	0 (0.0%)	
	without a history	160 (61.1%)	56 (100%)	70 (93.3%)	
Menstrual cycles	irregular	153 (58.4%)	15 (26.8%)	12 (16%)	<0.0001
	regular	109 (41.6%)	41 (73.2%)	63 (84%)	
Ovarian abnormalities	ovarian fibroids	5 (1.9%)	3 (5.4%)	5 (6.7%)	<0.001
	polycystic ovary	14 (5.3%)	4 (7.1%)	8 (10.7%)	
	PCOS	87 (33.2%)	10 (17.9%)	6 (8%)	
	a single ovary	1 (0.4%)	1 (1.8%)	1 (1.3%)	
	without anomalies	155 (59.2%)	38 (67.9%)	55 (73.3%)	
Anomalies Uterine	uterine fibroid	40 (15.3%)	5 (8.9%)	21 (28%)	<0.0001
	uterine deformity	10 (3.8)	0 (0%)	0 (0%)	
	tubal obstruction	5 (1.9%)	5 (8.9%)	0 (0%)	
	without anomalies	207 (79%)	46 (82.1%)	54 (72%)	

The association between the studied hormones and the vitamin D status is described in Table 3. A significant relationship between these two parameters was noted with the level of FSH, progesterone and estrogen (P χ^2<0.05 for FSH, P χ^2<0.0001 for progesterone and estrogen). In contrast, the LH level results were insignificant (P χ^2>0.05).

Table 3. Relationship of vitamin D status with hormonal profile

		Vitamin D status			P Value
		Deficiency	Insufficient	Normal	
FSH (mUI /ml)	Mean±SD	4.7±2.74	5.03±1.79	7.06±2.16	<0.0001
	Low	46 (17.6%)	5 (8.9%)	5 (6.7%)	0.038
	High	5 (1.9%)	0 (0.0%)	0 (0.0%)	
	normal	211 (80.5%)	51 (91.1%	70 (9.3%)	
LH (mUI/ml)	Mean±SD	2.37±1.81	2.19±1.29	2.84±1.65	0.062
	Low	40 (15.3%)	5 (8.9%)	5 (6.7%)	0.109
	High	5 (1.9%)	0 (0.0%)	0 (0.0%)	
	normal	217 (82.8%)	51 (91.1%)	70 (9.3%)	
Progesterone (µg/l)	Mean±SD	0.25±0.22	0.37±0.44	1.18±0.32	<0.0001
	Normal	165 (63%)	36 (64.3%)	75 (100%)	<0.0001
	Low	97 (37%)	20 (35.7%)	0 (0.0%)	
Estrogen (pg/ml)	Mean±SD	89.81 ±66.55	146.61 ±81,13	146.02 ±42.04	<0.0001
	Normal	165 (63%)	36 (64.3%)	75 (100%)	<0.0001
	Low	97 (37%)	20 (35.7%)	0 (0.0%)	

Hormonal assessment showed that abnormal levels were mostly found in the deficient vitamin D group than in those with normal levels of this vitamin (Table 3). In addition, we found a positive correlation between vitamin D levels and FSH, progesterone and estrogen hormones (P<0.0001) (Figure 1A, B, C). This was similarly so with kLH, but without significance (P>0.05) (Figure 1D).

Our study revealed that an important number of patients suffering from hypovitaminosis D were supplemented with vitamin D (171 cases), while 222 women had not complied with this vitamin supplementation. Vitamin D3 dosage in most of patients was of 200,000 IU with an interval of 15 days, only 11 cases (4.2%) complied with a regulated treatment regimen for 6 months and two therein had a pregnancy (Table 4). The correlation between vitamin D and the duration of supplementation revealed that more that

Table 4. Relationship of vitamin D status with data on Vitamin D supplementation

		Vitamin D status			P Value
		Deficiency	Insufficient	Normal	
Vitamin D supplementation	Yes	144 (55%)	26 (46.4%)	1 (1.3%)	<0.0001
	No	118 (45%)	30 (53.6%)	74 (98.7%)	
Duration of supplementation (months)	Mean±SD	0.76 ±1.203	0.5 ±0.57	0.01 ±0.11	<0.0001
	Unsupplemented	118 (45%)	30 (53,6%)	74 (98.7%)	<0.0001
	≥ 1 month	133 (50.8%)	26 (46.4%)	1 (1.3 %)	
	2-3 months	0 (0%)	0 (0%)	0 (0%)	
	4-6 months	11 (4.2%)	0 (0%)	0 (0%)	
Post-supplementation observation	Pregnancy	2 (0.8 %)	0 (0%)	0 (0%)	<0.001
	Without-results	142 (99.2%)	56 (100%)	75 (100%)	

the level of vitamin D increased, the greater the decrease in supplementation duration (P<0.0001) (Figure 1F).

DISCUSSION

Our study revealed a predominance of hypovitaminosis in our infertile patients, which indicates a clear link between normal vitamin D status and improved fertility. Indeed, the role of vitamin D3 in the female reproductive tract has been extensively investigated because its receptor is abundant in reproductive organs, including the ovary. Of note, the expression of vitamin D3 receptor in the ovary is as an extra-renal site. Furthermore, the influence of vitamin D3 on follicular development and ovarian steroidogenesis has been investigated [11].

Bhattarai *et al,* [1] stated that vitamin D synthesis is also influenced by age (decreased production capacity). The elderly, particularly those living in institutions, represent a population with a higher risk of vitamin D deficiency (low exposure, increased needs and production of urine, as well as a decrease in dietary vitamin D, renal production, VDR level.

In Algeria, the prevalence of female obesity in 2013 was estimated at 30.1% [12]. Data from meta-analyses consistently support an inverse association of vitamin D levels with body weight [13] and that low vitamin D intake could be an obesity major predictor. This stated outcome is similar to our results. Up today, it is not clear if vitamin D insufficiency is a consequence of obesity or the situation is reversed. Recent findings have stated that volumetric dilution of vitamin D is the most frequent mechanism of the inverse relationship between serum vitamin D levels and BMI. Although obese and lean subjects have similar amounts of VD, in overweight individuals, VD is distributed in a larger volume, making serum concentrations lower. Of note, 25(OH)D is distributed mostly in serum, muscles, fat and liver – and organs that are more important in cases of obesity [14].

Our study revealed a significant association between residence and vitamin D status, with rural women being less deficient in vitamin D than women from urban areas. Indeed, direct sunlight exposure is more noted in rural regions than in urban areas. Vitamin D is the sunshine vitamin. When exposed to the sun, the 7-dehydrocholesterol found in the skin absorbs ultraviolet B (UVB) rays and converts them into pre-vitamin D3. As pre-vitamin D3 is thermodynamically unstable, it isomerizes within a few hours to form vitamin D3. The body has a great capacity to produce vitamin D3, and reasonable exposure to sunlight can enhance 25-hydroxyvitamin D blood levels [15].

Fung *et al.,* [16] indicated that poor levels of 25(OH)D are associated with a 76% reduction in the chances of pregnancy. These data explain the significant inverse correlation between the vitamin D level and infertility duration noted in our study.

There are several studies [17,18] correlating low 25(OH) D status with PCOS characteristics, which is consistent with our results. Interestingly, in 2019, epidemiological studies in Algeria noted 499,279 cases of PCOS [19]. Vitamin D has been suggested to play an important role in PCOS with regard to several aspects, including menstrual regularity, fertility, BMI, lipid profile, insulin resistance and cardiovascular risk [18].

Furthermore, the effects of vitamin D can also be explained by its immunomodulatory power. Indeed, different alterations can be observed in cases of vitamin D deficiency such as dominance of Th2 cytokines [20] and reduction in the production of inflammatory cytokines [21]. Additionally, vitamin D has been shown to inhibit the production of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interferon-gamma (IFN-γ) and increase the production of human chorionic gonadotropin (hCG) in the trophoblast in vitro [22].

The normal level of Vitamin D was predominant in women with endometriosis, which is not consistent with other studies [23,24] that observed an association of low levels of 25(OH)D with a significantly increased risk of endometriosis. This data can be justified by the small number of cases of endometriosis in our study and the genetic predisposition. Two elements argue in favor of a potential relationship of vitamin D and endometriosis based on the expression of VDR in the endometrium [25].

We found a significant association between vitamin D and miscarriage, which was confirmed by other studies showing that the human placenta is a key tissue for the accumulation of 25(OH)D and 1,25-dihydroxy vitamin D active (1,25(OH)2D) [26], with the potential to exert significant effects on trophoblast invasion, remodeling of the placental spiral artery and function of immune cells [27]. These processes are altered in human miscarriages, with aberrant endometrial receptivity and dysregulated placentation noted shortly after initial conception [28,29]. It is, therefore, possible that a low serum level of 25(OH)D contributes to the physiology of miscarriage through a concomitant decrease in placental 1.25(OH)2D level and the resulting placental dysregulation [30].

The expression of vitamin D receptors in the endometrium and the role of vitamin D in the transcription of the HOX10A gene (which has been shown to be important in implantation) suggest that the immunomodulatory effects of vitamin D could have a direct impact on implantation and, hence, the probability of success of reproductive treatment [31], which explains the relationship between vitamin D deficiency and abortion.

According to the conclusions of a study by Li *et al* [32], women with normal vitamin D rates are less likely to have fibroids than others, which is in agreement with our results.

Regarding ovarian steroid genesis, human ovarian cells trigger progesterone and estradiol secretion in the presence of calcitriol [30]. This may confirm the significant correlation found between estrogen, progesterone – and vitamin D (P<0.0001). Other experimental studies [33] reported an influence of the metabolites of vitamin D on the production of reproductive hormones. Indeed, granulosa cells contain vitamin D receptors (VDR), and *in vitro* stimulation of human ovarian cells by 1,25(OH)2 D (1,25-dihydroxy vitamin D) affects ovarian steroidogenesis [34].

The experimental effect of vitamin D on estrogens is, however, clearer. Studies on human granulosa cells [35] porcine [36] and caprine [37] have revealed a stimulating

effect of 1,25(OH)2 D3 on estradiol (E2) and aromatase enzyme.

Kolcsár *et al.,* [31] found that serum 25-hydroxy vitamin D levels of approximately 20 ng/mL may be necessary to trigger ovulation or to support progesterone secretion. This explains the significant relationship between progesterone and vitamin D in our study.

The chi-squared and ANOVA test showed a significant relationship between FSH and vitamin D, which is consistent with literature findings [38] that claimed that vitamin D can also play a role in modulating FSH sensitivity and selecting dominant follicles in granulosa cells, through down-regulation of the FSH receptor. On the other hand, no significant relationship was found between LH and vitamin D.

Supplementation should be individualized based on measured concentration (give more vitamin D to those with lower concentrations) [39]. After an initial dosage of 25OHD, a regimen of 50,000 IU per week for eight weeks in those with a 25OHD concentration <20 ng/mL, or 50,000 IU weekly for four weeks in those with a 25OHD concentration between 20 and 30 ng/mL is recommended. This rapid "recharge" period should then be followed by a maintenance treatment of 50,000 IU/month. The effectiveness of this should be evaluated after 3 to 6 months by measuring the 25OHD and possibly readjusting the dosage. If the 25OHD is still <30 ng/mL, dose interval could be reduced, i.e: 50,000 IU every 2 weeks, or an increased dosage (for example: 80,000 or 100,000 IU per month) applied [39]. Our patients did not respect this therapeutic regimen, which explains the absence of positive results after supplementation.

CONCLUSION

If vitamin D is fundamental for good fertility and increased pregnancy, it is partly due to its contribution to the induction of sex hormones production by the body, the improvement of the menstrual cycle, and its beneficial effects on the characteristics of PCOS and other conditions associated with female infertility. Thus, good control of vitamin D levels is important for improving female fertility.

LIMIT

Some patients refused to participate in the study or sign their consent, others did not have the full evaluation of biological analyses, particularly vitamin D, due to its expensive price.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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