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The impact of serum vitamin D on fertility status in a sample of Iraqi women

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Background: The existence of vitamin D metabolizing enzymes and receptors in female tissues of reproductive origin has been documented by a list of studies. In addition, low levels of vitamin D have been observed in women with polycystic ovary syndrome with sub-fertility, and vitamin D supplementation for those women has been associated with improved menstrual irregularities, metabolic derangements, and fertility outcomes.

Aim of the study: The present case-control study was aimed at comparing the serum vitamin D level of a sample of subfertile Iraqi women to that of a control sample of pregnant women.

Subjects and methods: The current case-control study enrolled 54 subfertile women, and 50 fertile women recruited from the obstetrics and gynecology department at Pediatric and Maternity Teaching Hospital, Adiwaniyah Province, Iraq. The serum level of vitamin D was measured and compared between the two groups.

Results: The mean level of the subfertile group was higher in a significant manner when compared to that of the control group: 22.79 ± 4.64 ng/ml vs. 27.35 ± 8.60 ng/ml, respectively (p=0.001). In addition, the proportion of women in the subfertile group with vitamin D deficiency was higher than that reported in the control group, 40.0% vs. 25.9%, respectively, but this difference was not significant (p=0.126).

Conclusion: Low serum vitamin D is significantly linked to subfertility in Iraqi women during reproductive age. Therefore, we recommend adopting the strategy of vitamin D supplementation for Iraqi women during reproductive age to reduce the health burden of sub-fertility in our community.

Keywords: Sub-fertility; Iraq; Vitamin D; Deficiency

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INTRODUCTION

Deficiency and insufficiency of vitamin D have been linked during the past few decades to a number of health issues worldwide (1). For instance, vitamin D deficiency has been associated with autoimmune disorders, cardiovascular disorders, malignant diseases, obstetric complications, musculoskeletal defects, degenerative neurological abnormalities, and fertility issues [1-3]. Evidence about the association between vitamin D insufficiency and fertility physiology has been withdrawn from experimental studies on animal models as well as a number of clinical trials [3-5]. The role of vitamin D was demonstrated to modulate reproductive activities in both men and women [6–8].

The existence of vitamin D metabolizing enzymes and receptors in female tissues of reproductive origin has been documented by a list of studies [4]. In addition, low levels of vitamin D have been observed in women with polycystic ovary syndrome with subfertility, and vitamin D supplementation for those women has been associated with improved menstrual irregularities, metabolic derangements, and fertility outcomes [9,10]. Moreover, the process of steroidogenesis concerning progesterone and estradiol in women has been shown to be influenced by vitamin D, and lower levels of serum vitamin D were associated with subfertility [11].

Recent research on vitamin D in the Middle East has delved into its impact beyond calcium regulation, focusing on metabolic diseases like metabolic syndrome, hypothyroidism, and diabetes mellitus [12-14]. Human and animal studies linking vitamin D to fertility have focused on spermatogenesis, folliculogenesis, implantation rate, pregnancy rate, and endometrial thickness. The results of these studies were controversial, despite the overwhelming evidence supporting the role of vitamin D in human fertility [15-18]. The link between vitamin D and women's fertility needs further research in our country because of the cultural issue relating to the pattern of female dressing necessitating covering almost the whole body, making the sun exposure, which is by far the most important source of vitamin D production, difficult.

In addition, research work on this issue is still limited in Iraq. Therefore, the present case-control study was aimed at comparing the serum vitamin D level of a sample of subfertile Iraqi women to that of a control sample of pregnant women.

SUBJECTS AND METHODS

The current study was designed according to the case-control pattern of observational studies. The cases were 54 subfertile women. The inclusion criteria were: infertile women with primary or secondary infertility aging between 18 and 40 years; women with female factors of infertility or an unexplained cause; and women without a history of chronic medical illness in addition to a normal basal FSH level (≤ 14 mIU/mL). The exclusion criteria were: women older than 40 years; women with a history of male factor infertility or chronic medical illness; and women refusing to be enrolled in the study. Control cases were 50 fertile women with an age range of 18 to 40 years without a history of any chronic medical illness. Those women were recruited from obstetrics and gynecology department at Pediatric and Maternity Teaching Hospital, Adiwaniyah Province, Iraq. The period of study extended from January 2023 to December 2023. Ethical approval for this study was issued by the ethical committee for clinical research belonging to University of Al-Qadisiyah. Participants were all asked to give written consent to be enrolled in this study.

Data collection

Variables include demographics (age and body mass index), types, and causes of infertility. Responses to the following questions were reported: do you practice exposure to the sun daily and regularly for at least 30 minutes per day, and do you eat vitamin D-rich food items regularly? Blood samples were withdrawn from each participant and sent to the laboratory of the hospital in order to measure serum vitamin D levels and serum hormonal levels, including cycle day 2 estradiol, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin hormone, Thyroid Stimulating Hormone (TSH), and Anti-Mullerian Hormone (AMH). Serum 25 (OH) vitamin D was assessed using Cobas e602 (Roche Diagnostics, Mannheim, Germany) using an immunoassay with ElectroChemiLuminiscence (ECL) technology with a lower detection limit of 4 ng/ml. In this study, vitamin D deficiency was considered at serum levels of less than 20 ng/mL [19]. Serum hormones were measured on a Roche-Elecsys 2010 (Germany) analyzer based on the principle of electrochemiluminescence immunoassay.

Data analysis

Data was analyzed using SPSS version 23.0 (SPSS, Chicago, IL, USA). Frequencies were presented as percentages (%) and continuous variables were presented as mean ± standard deviation. Chi-square was done to elicit differences in frequencies between cases and controls. Independent t-test was done to compare differences among continuous variables. Significance was set at p ≤ 0.05.

RESULTS

The demographic characteristics of the women enrolled in the study are shown in **Tab. 1.** The mean age showed no significant difference (p=0.575) when contrasted between the sub-fertile group and the control group, 28.28 ± 4.09 years *vs.* 28.74 ± 4.25 years, respectively. There was also no significant difference in mean Body Mass Index (BMI) (p=0.135) between study groups, 28.86 ± 3.43 kg/m^2 *vs.* 27.67 ± 4.53 kg/m^2, respectively. With respect to type of infertility, the subfertile group included 29 (58.0%) women with primary infertility and 21 (42.0%) women with secondary infertility; the control group included 32 (59.5%) women with primary infertility and 22 (40.7%) women with secondary infertility. There was no significant difference in the proportions of types of infertility between study groups (p=0.896). In addition, there was no significant difference in mean duration of infertility between study groups (p=0.800), 3.51 ± 1.53 years *vs.* 3.59 ± 1.76 years, respectively.

Responses to questions assessing vitamin D acquisition habits are shown in **Tab. 2.** Responses to the question "Do you practice exposure to the sun daily and regularly for at least 30 minutes per day?" showed no significant variation between the sub-fertile group and the control group (p=0.633), and the "yes" response was reported as

Tab. 1. Demographic characteristics of women enrolled in the study.

Characteristic	Sub-fertile group *n* = 50	Control group *n* = 54	*p*
Age (years)			
Mean ± SD	28.28 ± 4.09	28.74 ± 4.25	0.575 I NS
Range	20 -35	22 -35	
BMI (kg/m^2)			
Mean ± SD	28.86 ± 3.43	27.67 ± 4.53	0.135 I NS
Range	20 -35	20 -40	
Normal weight	1 (2.0 %)	6 (11.1 %)	-
Overweight	22 (44.0 %)	24 (44.4 %)	-
Obese	27 (54.0 %)	24 (44.4 %)	-
Type of infertility			
Primary	29 (58.0 %)	32 (59.3 %)	0.896 C NS
Secondary	21 (42.0 %)	22 (40.7 %)	
Duration of infertility (years)			
Mean ± SD	3.51 ± 1.53	3.59 ± 1.76	0.800 I NS
Range	1 -8	1 -8	

SD: Standard Deviation; I: Independent samples t-test; C: Chi-square test; NS: Not Significant; ***: significant at p ≤ 0. 001

38.0% and 42.6% in the groups, respectively. Responses to the question "Do you eat vitamin D-rich food items regularly?" showed no significant variation between the sub-fertile group and the control group (p = 0.640), and the "yes" response was reported as 78.0% and 74.1% in the two groups, respectively.

Serum hormonal levels are shown in **Tab. 3.** There was no significant difference in mean serum hormonal levels between the sub-fertile group and the control group (p>0.05). The serum vitamin D level contrasted between the subfertile group and the control group is shown in **Tab. 4.** The mean level of the subfertile group was higher in a significant manner when compared to that of the control group: 22.79 ± 4.64 ng/ml *vs.* 27.35 ± 8.60 ng/ml, respectively (p=0.001). In addition, the proportion of women in the subfertile group with vitamin D deficiency was higher than that reported in the control group, 40.0% *vs.* 25.9%, respectively, but this difference was not significant (p=0.126).

DISCUSSION

The problem of vitamin D deficiency has been recently discussed in Iraqi medical literature, and it has been linked to a number of medical conditions [20]. This problem in Iraqi women within the reproductive age range has been linked to religious and cultural behaviors relating to women dressing in such a way that it limits sun exposure, which is a major source of vitamin D [21]. 1. Nevertheless, despite this explanation, the majority of Iraqis make an effort to steer clear of direct sunlight due to the extreme heat in the area (exceeding 50 °C in the summer, which lasts a considerable length of time). This underscores the necessity for further research on the impact of vitamin D deficiency on fertility in Iraq [20].

In addition, the problem of infertility is becoming increasingly recognized in our community [20]. Linking infertility to vitamin D deficiency in Iraqi women has been studied, and a statistically significant impact has been

Tab. 2. Response to questions assessing vitamin D acquisition habits.

Characteristic	Sub-fertile group *n* = 50	Control group *n* = 54	*p*
Do you practice exposure to sun daily and regularly for at least 30 minutes per-day			
Yes	19 (38.0 %)	23 (42.6 %)	0.633 C NS
No	31 (62.0 %)	31 (57.4 %)	
Do you eat vitamin D rich food items regularly			
Yes	39 (78.0 %)	40 (74.1 %)	0.640 C NS
No	11 (22.0 %)	14 (25.9 %)	

C: Chi-square test; NS: Not Significant

Tab. 3. Serum hormonal levels.

Characteristic	Sub-fertile group *n* = 50	Control group *n* = 54	*p*
Estradiol (E_2) (pg/ml)			
Mean ± SD	41.04 ± 23.42	37.95 ± 12.56	0.491 I NS
Range	11.79 -70.7	20 -68.75	
Follicle Stimulating Hormone (FSH) (mIU/ml			
Mean ± SD	6.41 ± 2.07	6.09 ± 1.54	0.270 I NS
Range	4.3 -9.2	1.78 -10.42	
Luteinizing Hormone (LH) (mIU/ml)			
Mean ± SD	5.13 ± 2.11	5.06 ± 2.32	0.237 I NS
Range	1.78 -9.3	0.31 -13.9	
Prolactin (ng/ml)			
Mean ± SD	16.59 ±7.19	14.85 ± 5.91	0.325 I NS
Range	5.2 -35.1	2.7 -30.05	
Thyroid Stimulating Hormone (TSH) (mIU/ml)			
Mean ± SD	2.05 ± 0.55	2.17 ± 0.81	0.508 I NS
Range	1.1 -3.2	0.75 -6.1	
Anti-Mullerian Hormone (AMH) (ng/ml)			
Mean ± SD	6.96 ± 1.93	6.41 ± 3.52	0.341 I NS
Range	4.04 -11.3	1.47 -10.84	

SD: Standard Deviation; I: Independent samples t-test; NS: Not Significant

Tab. 4. Serum vitamin D level contrasted between sub-fertile group and control group.

Characteristic	Sub-fertile group *n* = 50	Control group *n* = 54	*p*
Vitamin-D (ng/ml)			
Mean ±SD	22.79 ±4.64	27.35 ±8.60	0.001 I ***
Range	13.1 -30.8	13.6 -39.9	
Deficiency	20 (40.0 %)	14 (25.9 %)	0.126 C NS
No deficiency	30 (60.0 %)	40 (74.1 %)	

SD: Standard Deviation; I: Independent samples *t*-test; C: Chi-square test; NS: Not Significant; ***: significant at $p \leq 0.001$

observed [20]. In the present study, the mean level of serum vitamin D showed a significant difference between the subfertile group and the control group; the level was lower significantly in the subfertile group in comparison with the control group. In addition, we observed more frequent proportions of women with vitamin D deficiency (serum level of <20 ng/ml) to be associated with sub-fertility.

Nevertheless, we observed no significant difference in the habit of daily sun exposure or in the habit of taking vitamin D-rich food on a regular basis between the groups in the study. Therefore, vitamin D deficiency in women during reproductive age may be due to reasons other than sun exposure or dietary habits. There are reports that link vitamin D deficiency to genetic factors. Indeed, several observational studies have evaluated the association of Single-Nucleotide Polymorphisms (SNPs) in vitamin D-related genes and vitamin D levels [22]. For that reason, we recommend future studies be focused on the link between genetic influence and vitamin D serum levels in Iraqi subfertile women.

The significantly lower vitamin D level seen in the subfertile group is indeed in accordance with several previous reports [3,20]. Adequate levels of vitamin D are known to positively impact fertility and can potentially enhance the chances of a successful pregnancy. Numerous studies have associated vitamin D insufficiency with a higher probability of preterm birth, gestational diabetes, pre-eclampsia, and bacterial vaginosis [23-26].

The significance of vitamin D production at the feto-maternal interface is emphasized by the presence of α-hydroxylase in the decidua and placenta [27-29]. In general, vitamin D supports placental growth and function by regulating placental calcium transport and displaying immunomodulatory effects, which are crucial for sustaining pregnancy [30]. During early pregnancy, the rapid appearance of VDR and α-hydroxylase CYP27B1 in the decidua and placenta plays a vital role in the role of vitamin D in development, including implantation and placental growth [31-33]. Vitamin D binding to VDR has been demonstrated to regulate key target genes, such as HOXA10, that are necessary for endometrial development, uterine receptivity, and implantation [34,35].

CONCLUSION

Low serum vitamin D is significantly linked to subfertility in Iraqi women during reproductive age. Therefore, we recommend adopting the strategy of vitamin D supplementation for Iraqi women during reproductive age to reduce the health burden of sub-fertility in our community.

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CONFLICT OF INTEREST

No conflict of interest is to be declared by the authors of this study.

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