

Effect of Vitamin D in the Resolution of Menorrhagia and Irregular Menstrual Cycle

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ABSTRACT

Rational of Vitamin D (Vit.D) is responsible for the regulation of various biological activities, it has an essential role in neurohumoral regulation of the hypothalamic-pituitary-ovarian system thus Vit.D deficiency is associated with menstrual disorder. The current study aimed to check the efficacy of Vit.D in women regarding the gynecological problem. A longitudinal interventional research study was performed to collect the data from an obstetrics and gynecology outpatient clinic in Mosul City, Iraq. Fifty participants aged between 12 and 47 years were participated in the current study, from the period of 1st December 2019 to the 1st December 2020. These reproductive women have gynecological problems with Vit.D deficiency, 25 (OH) D levels ($LD < 30 \text{ ng/mL}$). The participants received once weekly dose of 50 000 IU orally for two months. After this period of treatment, there was a significant elevation in serum Vit.D level $p < 0.0000$ and significant relief of their gynecological problem (irregular menstrual cycle, menorrhagia) ($p < 0.000$, $p < 0.0000$) respectively. An administration of once weekly dose of 50 000 IU orally for two months in patients with gynecological problems (irregular cycle, menorrhagia) and Vit.D deficiency could improve these gynecological problems were observed.



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1. INTRODUCTION

Vit.D is a calcemic vitamin, and it is a hormone of pleiotropic effects on extraskeletal target tissues, deficiency in Vit.D deficiency is one of the etiological factors associated with the development of several diseases, including musculoskeletal system diseases, Diabetes Mellitus, male and female genital system disease, central nervous system disease cardiovascular diseases and cancer [1- 3]. Inadequate sun exposure and decrease dermal production of 7-dehydrocholesterol, and limited food intake and supplements are considered the etiology of Vit.D deficiency, this deficiency interferes with the role of all body systems and enhances the porosity of the bone, malignancy, heart disease, autoimmune diseases, and mental disorders

such as depression. Chronic pain [4], [5]. Vit.D has essential responsibilities for female reproduction, perhaps in its effects on calcium homeostasis, fluctuations in the sex steroid hormone cycle, or the role of neurotransmitters [6]. Vit.D undergoes hepatic hydroxylation to form 25 hydroxyvitamin D (25 (OH) D₂ or 25 (OH) D₃), the main form of circulation which has little biological activity. The kidney converts 25 (OH) D into its bioactive hormone metabolite 1,25 dihydroxy Vit.D (1,25 (OH) D₂ or calcitriol) by 25 (OH) D-1 alpha-hydroxylase (CYP27B1). The nuclear Vit.D receptors mediate the main effects of 1,25 (OH) D₂ [7].

Vit.D is responsible for the regulation of various biological activities and mediates diverse regulatory mechanisms related to numerous organs; it exerts its effects through its affinity binding to Vit.D receptors which are located in the nucleus of body tissues and organs including the reproductive system and pituitary gland, thereby, have an essential role in neurohumoral regulation of the hypothalamic-pituitary-ovarian system thus Vit.D deficiency is associated with the menstrual disorder, and there is evidence indicates that there is a relationship between this vitamin and reproductive health [8], [9].

The abnormal condition in a woman's menstrual cycle includes a broad range of physical symptoms such as Menorrhagia (too much menstrual blood flow); Dysmenorrhea (menstrual cramps); irregular, recurrent, and more prolonged periods; Oligomenorrhea (light menstrual period); and amenorrhea (missed menstrual period) [10]. Menorrhagia is a health care problem; it affects about 30 percent of women during a woman's childbearing years [11], which means menstrual blood loss of 80 ml or higher each menstrual period [12]. The etiology for Menorrhagia may occur either from various diseases, including uterine fibroids, endometriosis, leiomyoma, or may occurs in the absence of any secondary disease, thus called dysfunctional uterine bleeding [13]. Approximately 50% of cases occur due to unidentified causes [11]. Severe menstrual bleeding can affect a woman's quality of life, including social, physical status, psychological status [12].

The prevalence of Menorrhagia in most women is occurred by changes in the local microendometrial environment, which is involved in the hemostatic mechanism of the endometrium [14].

2. Materials and Methods

This longitudinal interventional clinical follow-up-based study was conducted on 50 childbearing-aged women who presented to the outpatient clinic of Obstetrics and Gynecology. The study included these reproductive women who have gynecological problems with Vit.D deficiency (levels of Vit.D [25 (OH) D] < 30 ng/mL) these women had the following inclusion criteria: reproductive-age women with Gynecological problem (menorrhagia, irregular menstrual cycle), women with the uterine disease; fibroids, endometriosis or others, renal, liver or cardiovascular disease, hypertension, women recently used hormonal contraceptive agents or any drugs that interfere with menstrual cycles are excluded from the study. The parameter of choice for the measurement of Vit.D condition is serum 25-hydroxy vitamin D [25 (OH) D] concentration. In recent times, numerous studies have used 30 ng/mL as a cut-off value, and the majority of experts now recommend the normal level of 25-hydroxy vitamin D [25 (OH) D] to be ≥ 30 ng/mL [15]. Liquid chromatography-tandem mass spectrometry was used to obtain the Concentrations of Vit.D as 25 (OH) D. Samples were determined in duplicate.

3. Statistical Analysis

Data collected in this study has analyzed with the Statistical Package for Social Sciences (SPSS) program (version 25), The standard statistical method used to determine the average and standard values deviation ($M \pm SD$), paired student t-test used for comparing the level of Vit.D. A probability value (p-value) < 0.05, considered statistically significant.

4. Result

Fifty reproductive age women range between (12-47) years with a mean 33.20 ± 6.77 years were included in this study, and mean Vit.D level is 9.42 ± 3.09 , most of the studied patients 43 (86%) were married while only 4 (8%) were single, 3 (6%) were Widowed (Table 1). 32(64%) of the studied patients have irregular menstrual cycle 11 (22%) of the studied patients were presented with menorrhagia, while 1 (2%) have amenorrhea.

All of the studied patients have received Vit.D treatment, including weekly high-dose oral supplements (50,000 IU) of Vit.D for eight weeks and significant change in their serum concentration ($p < 0.0000$) as well as a significant improvement of irregular menstrual cycle and menorrhagia ($p < 0.0000$, $p < 0.0000$) respectively were seen (Table 2).

Table 1: Demographic distribution of patients.

Women enrolled (50)	
Age (years)	Mean \pm SD
	33.20 ± 6.77
Marital status No (%)	
Single	4 (8%)
Married	43 (86%)
Widowed	3 (6%)
Irregular cycle	32(64%)
Menorrhagia	11(22%)
Vit.D blood level	9.42 ± 3.09

Table 2: Effect of Vit.D supplement on Gynecological problem.

Parameter		Before treatment (No.)	After treatment (No.)	P-value
Menstrual cycle	Irregular	32	0	0.000* (s)
	Regular	18	50	
Menorrhagia	Yes	11	0	0.00004* (s)
	No	39	50	
Vit.D		9.42 ± 3.09	36.42 ± 3.39	0.0000* (s)

5. Discussion

There are modest studies that established the role of Vit.D as a supplement for the regulation of the menstrual cycle, therefore this study was performed to support other studies. The result of the current research revealed that the use of Vit.D for two months of therapy among reproductive women with menstrual disorder was associated with a significant increase in serum Vit.D concentration ($p < 0.0000$) as well as considerable improvement of the irregular menstrual cycle and menorrhagia ($p < 0.0000$, $p <$

0.0000) respectively. These results in agreement with the results of many researchers [16- 18] in their study show that Vit.D deficiency has a role in the progress of menstrual disorders in reproductive women. These findings were from the previous study by [19]. who found that menstrual cycles disorder is five times higher in women who were less than 30 ng/mL of 25 (OH) D than women who were more than 30 ng/mL. There is an interaction between Vit.D and menstrual cycle disorder, Vit.D has a crucial function in the ovary and regulation of the menstrual cycle [20]. In concordance with these results, the study of [16], who found that the lower concentration of 25 (OH) D in reproductive women correlated with an irregularity of menstrual cycle, this result has ascertained by [21]. [6], [22] in their study also confirm that Vit.D supplement was related to a diminution in the occurrence of diverse menstrual symptoms.

It is now well established that Vit.D activates the Vit.D receptor and enhance the expression of about three thousand genes in different tissue types, including female reproductive tissues [23]. The reduction of menorrhagia by Vit.D supported the concept that the heavy menstrual cycle is mediated by disorder in expression and signaling of the endometrial mediators [24]. Numerous physiological attention has been explained by the intensive flow of blood during the menstrual cycle, which is either of the primary origins or induced by endometrial pathogenesis. Prostaglandins (PG) act locally within endometrial tissues to influence the onset of menstruation and may due to extensive menstrual blood loss. PG receptors may be involved in the maintenance of lysosomes which in sequence leads to enhanced release of multiple proteinases. These dynamics may change the hemostatic mechanism of the endometrium [20]. The endometrial angiogenic Factors signaling to participate in the development and maintenance of vascular homeostasis, thus the synthesis of PGE₂ and PG E binding sites are higher in endometrial tissue of reproductive women which complain from menorrhagia than women with normal menstrual period and show a direct relationship with sever menstrual loss [24], [25].

Disturbances in expression and signaling of endometrial mediators enhance menorrhagia, the endometrial tissue produces mainly PGF, and PGE₂ with smaller amounts of PGI₂ and thromboxane (TX) A₂. TXA₂; and PGF, are vasoconstrictors while PGI₂, and PGE₂, have the opposite effect of vasodilation. TXA is also a promoter of platelet aggregation while PGI₂ acts as an inhibitor of platelet aggregation. The interaction between the PG helps in the control of blood loss during menstruation and shifts in the production of these peptides to ones of vasodilatory has been suggested as important in the pathogenesis of menorrhagia [26]. Elevation of these vasodilatory factors may further exacerbate menstrual blood loss and vascular dysfunction by increasing production of the key molecules cyclooxygenase (COX), the enzyme responsible for the synthesis of PG, and promoting the expression of specific factors responsible for endometrial hemostasis (such as vascular endothelial growth factor) [27]. PG rise the expression of the COX-2 enzyme, metabolism of arachidonic acid, and generation of prostanoid [28]. endometrial cell expression of the diverge molecules of the COX-PG signaling pathways regulate menstruation process, elevated endometrial cell signaling found in women with menorrhagia [29]; therefore inhibition of the COX enzyme has been associated with decrease menstrual bleeding [24].

Besides, enhancement of the production of angiogenic factors such as basic fibroblast growth factor and vascular epithelial growth factor and angiopoietins, reduction of the production of antiangiogenic factors such as thrombospondin, angiostatin, and endostatin that are known to have specific effects on blood vessels, thus elevation in the of COX enzymes and endometrial PG receptors associated with causing vasodilation [24]. Increasingly, Nitric oxide is an endogenous compound that interacts with 25 (OH) D to enhance different metabolic pathways [30]. The presence of nitric oxide synthetase, the enzyme responsible for the synthesis of nitric oxide within the endometrial cell has led to suggestions that nitric oxide has a remarkable role in the local control of endometrial function, including the menstruation process. Its platelet

aggregation inhibitor, vasodilator, and is an essential mediator of paracrine interactions, therefore this metabolic factor can be involved in the onset and control of menstrual bleeding and establish the severity of menstrual bleeding [26].

The endometrium undergoes regeneration during menstruation. This is largely controlled by local factors such as angiogenic growth factors, matrix metalloproteinases, and macrophages, conflict in this process may contribute to changes in the volume of menstrual blood loss and contribute to the pathogenesis of heavy menses [26].

It has been recognized that calcitriol has a numerous physiological role in the regulation of body process, calcitriol inhibits the action of PG by different mechanism; reduce the expression of COX-2, which is responsible for PG synthesizes, enhance the production of 15- PG dehydrogenase, which inhibit the activates of PG and decreasing the synthesis of PG receptors that are responsible for PG signaling [31]. Very few different clinical outcomes have been documented in the literature about the effects of Vit.D supplementation [32], in their study, reported That there is no clinically positive correlation between Vit.D and the function of the reproductive organs.

To sum up, the present study showed a favorable improvement in menorrhagia and menstrual cycle disorder in reproductive women.

6. Conclusion

Vitamin D supplementation improves the gynecological problems (irregular cycle, menorrhagia) in women with low levels of Vit.D, it is recommended in women with Vit.D deficiency in order to achieve its effect in regulating menstrual disorders. Further studies are required to investigate the mechanism of improvements. Despite the strong correlation between Vit.D and good health, Vit.D deficiency is not recognized by a large number of women in the community, and a better understanding of this medical disorder is essential.

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