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Efficacy of Vitamin D3 Insufficiency Treatment on Pregnancy Rate: Clinical Trial

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ABSTRACT

Back ground: Vitamin D3 insufficiency is an essential factor effect on many body systems and mechanisms via the receptors of vitamin D3 (VDR) which is found in multiple organs, one of them is reproductive systems affecting the fertility of women.

Objectives: Management of vitamin D3 insufficiency can ameliorate pregnancy rates in the subfertile females.

Patients and Methods: This is a randomized interventional clinical trial. In which Serum vitamin D3-25-(OH) level of 90 women who had undergone fertility treatment cycle was checked. 86 women with insufficient serum vitamin D (< 30 ng/ml) were included in our analysis. 43 females were managed with 50000 IU vitamin D3, supplementation weekly, for six to eight weeks (group I) and 43 females without treatment (group II-control). Pregnancy rate represent our outcome.

Results: Our trial show significant statistical increase in the pregnancy rate (44.26%) in subfertile female after vitamin D3 supplementation (p=0.0007) and RR (relative risk)=3.7999.

Conclusion: Management of vitamin D insufficiency is significantly improved pregnancy rate of subertile women.

Keywords: Vitamin D, Subfertility, Pregnancy Rate.

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INTRODUCTION

The World Health Organization (WHO) estimated that about 10-25% of married people have subfertility disorder. subfertility affects approximately 80 million of people across the world (1). Vitamin D is a steroidal hormones acts in the nucleus via binding its nuclear receptors. The physiologic function of vitamin D; 1, 25-(OH)2, is to retain calcium homeostasis (2).Vitamin D have Important effect in reproductive physiology (3). Data supporting the correlation among reproduction and vitamin D shown in different investigations of the vitamin D receptors. Receptors of vitamin D are seen in different reproductive system organs, containing ovaries and uterus (4). The circulating concentration of the 25-(OH) vitamin D, is the universally applicated predictor of vitamin D3 status (2). In the past, a patient was considered deficient when vitamin D level was less than 10 ng/ml. Today, controversy exists. Most literature quotes levels <30 ng/ml as insufficiency (5). The prevalence of vitamin D insufficiency is high among reproductive age female and correlated with high risk of cancer, diabetes mellitus, autoimmune and cardiac diseases (4, 6).

More recently, hypovitaminosis D has been introduced to be as a associated factor to impair pregnancy outcomes and subfertility (7).

THE AIM OF THE STUDY

Management of vitamin D3 deficiency can ameliorate pregnancy rates in the subfertile target women.

PATIENTS AND METHODS

We conducted this randomized interventional clinical trial at private clinic in Al-kut city, Wasit, Iraq between September 2016 to April 2017. Informed verbal consent was obtained from all couples. Those with BMI >30 Kg/m2, history of endocrine disorders, severe endometriosis, systemic diseases, repeated abortion, congenital or acquired uterine anomaly with or without operation and also the patients who had visible hydrosalpinx in vaginal ultrasonography were excluded from our study. No female had previous history of vitamin D consumption. The level of Serum vitamin D of 90 women were checked. 4 females had sufficient serum vitamin D (>30 ng/ml). 86 women who their concentration of serum vitamin D was<30 ng/ml were included in our trial. The 86 patients were allocated into 2 groups by disclosing the sealed envelopes: vitamin D supplemented group(I) and the control group(II). The size of samples were defined 43 women in each group based on previous similar studious by statistician. One fasting venous blood sample (5 ml) was taken from each participant. Serum 25-hydroxy vitamin D level was measured with Roche-Cobas E411 Electro-chemiluminescence binding assay method. We considered patients insufficient or deficient; hear after refer to as insufficient; if they had serum vitamin D below 30ng/ml. 43 patients; as a vitamin D group I; received single dose 50000 IU vitamin D3 oral solution (equivalent to 2 vials of 25000 IU/2.5 ML oral solution ; Abiogen pharma, Italy) once weekly for 8-12 weeks, after the end of the treatment serum vitamin D level was rechecked at least 2 weeks. Another group II included of 43 patients; as a control group; were entered in ovulation induction cycle without any intervention.

In both groups the endometrium was prepared similarly. All women receive ovulation induction drugs Follicle Stimulating Hormone (FSH- rFSH serono, Switzerland as Gonal –F), Clomifene (clomid, 50 mg orally), Letrozole (Femara, 2.5 mg orally), 75 IU/ampoule Follitropine alfa, which were given intramuscularly or subcutaneously,

Human Chorionic Gonadotropin (HCG- pregnyl serono S.P.H, Italy, 5000-10000 IU). Luteal phase was supported by Duphastone tablets (10mg, Solvay pharmaceutical, Holland), and Folic acid tablet (5 mg/tab. SDI- Iraq). HCG was performed to confirm pregnancy, POSITIVE chemical pregnancy that was defined by serum B- hCG (IU/ml) level were > 10 IU/ml on day 14 post conception.

Statistical analysis

Our analysis was done by using Mstat 6.2.1.(Consolas 12, Segoe UI Semibold 10,4), Student's t test and chi-square test were carried out to detect the significant differences between two groups. The significance level was set at $p<0.05$.

RESULTS

In this analysis, we grouped both, patients with insufficient and deficient serum vitamin D level as insufficient. We found that vitamin D deficiency of highly prevalence. Only 4 women out of 90 women (4.44%) who checked serum vitamin D were sufficient i.e. 95.5% are deficient. 86 subfertile females with insufficient serum vitamin D (<30 ng/ml) were included in our study. 43 females were supplemented with vitamin D and 43 women received no supplementation. 86 women completed subfertility treatment cycle and included in the last analysis.

The mean of pretreatment serum vitamin D in the control group and in the vitamin D treated group were 6.4±3.5 and 6.3±4.5 respectively. The whole patients in vitamin D treated group had serum vitamin D (24.23±3.2) after treatment with vitamin D supplement.

1-Demographic Data of the Study Groups

Table 1: Baseline characteristics in vitamin D supplemented and control group

Variable		Vitamin D treated group (n=43)	Control group (n=43)
Age (years)		28.88±7.59	29.27±7.49
BMI (kg/m2)		25.85±2.33	25.24 ± 2.27
Type of infertility	Primary	36(83.72%)	28(65.11%)
	Secondary	7(16.28%)	15(34.88)
Duration of subfertility(years)		4.86±3.38	5.55±3.57
Pretreatment level of serum vitamin D, (ng/ml)		6.29±4.46	6.37±3.52
Values were expressed by % or mean± standard deviation.			

2-Prevalence of Severity of vit.D3 Deficiency in Our Group

We found high percentage of vit.D3 severely deficient i.e. less than 10 ng/ml (83.72%) comparing to insufficient i.e more than 10 ng/ml (16.27%).(Figure 1).

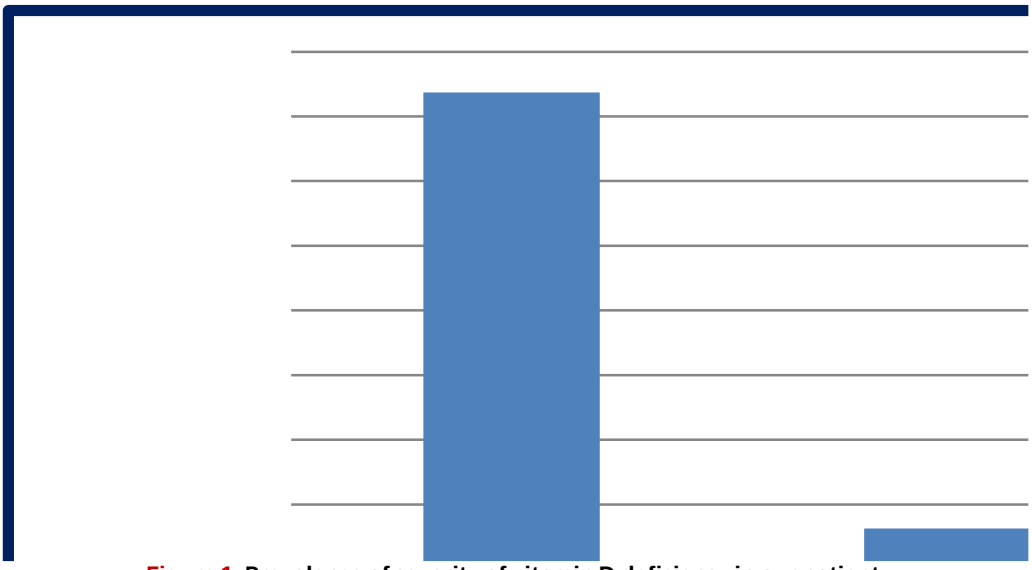

Figure 1: Prevalence of severity of vitamin D deficiency in our patient

3. Pregnancy Rate between 2 Groups According to vitD3 Supplementation

The pregnancy rate were in group I, II 44.26%, 11.63% respectively. There were statistical significant differences among groups including pregnancy rate(p=0.0007) and RR(relative risk)=3.7999 i.e positive association of pregnancy rates with vit.D supplementation. (Figure 2).

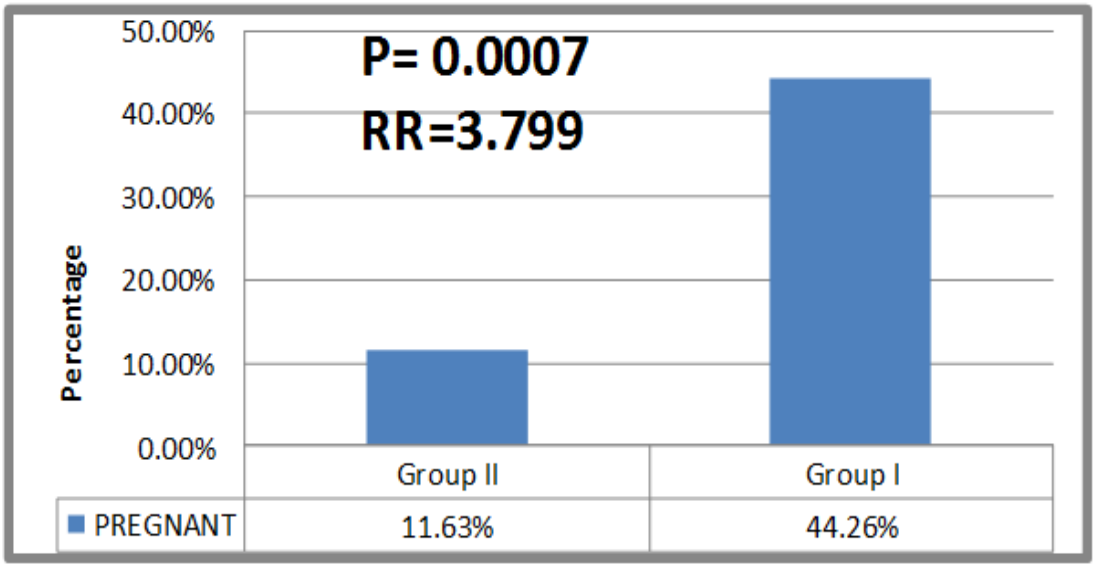

Figure 2: Pregnancy rate according to vit.D3 supplement

* Significance (P < 0.05), (RR>1). Group I (patient received vit.D supplement), Group II(control).

4. Pregnancy Rate between 2 Groups According to Age

A- < 35 years old.

B- ≥ 35 years old.

Although the pregnancy rate more in group A (66.3%) than group B(26.53%) and the pregnancy rate more in group I(71.33%) than group II (21.23%) but there were no statistical significant differences among groups including pregnancy rate(p=0.5). (Figure 3).

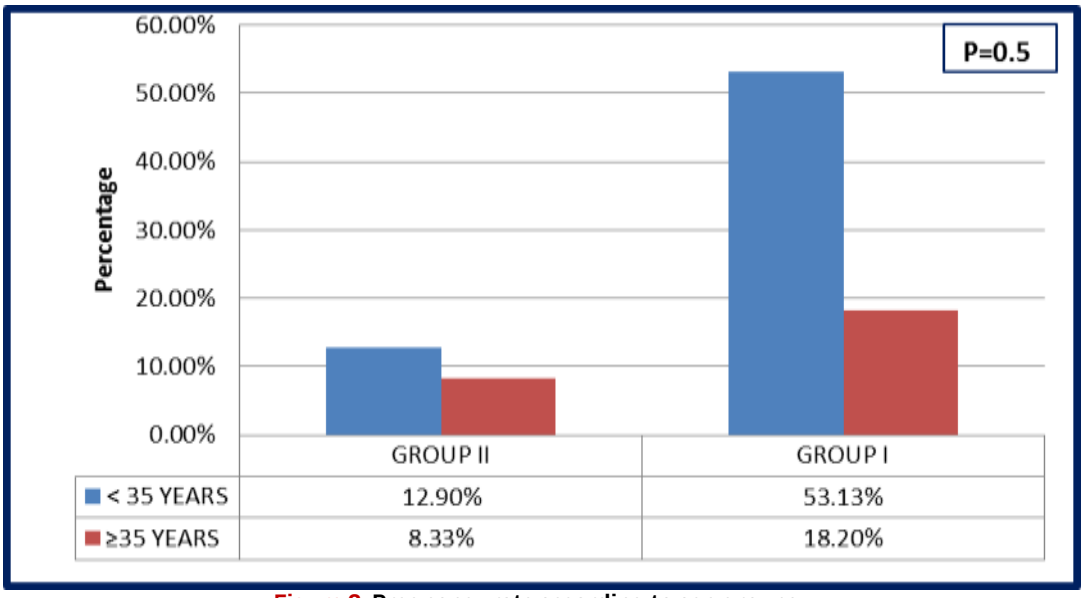

Figure 3: Pregnancy rate according to age groups.

*Significance (P < 0.05). Group I (patient received vit.D supplement), Group II (control).

5. Pregnancy Rate between 2 Groups According to the Level of vit.D Deficiency

A- < 10 ng/ml (severely deficient).

B- ≥ 10ng/ml (insufficient).

Although the pregnancy rate more in group B (91.7%) than group A(49.06%) and the pregnancy rate more in group I than group II but there were no statistical significant differences among groups including pregnancy rate(p=0.3). (Figure 4).

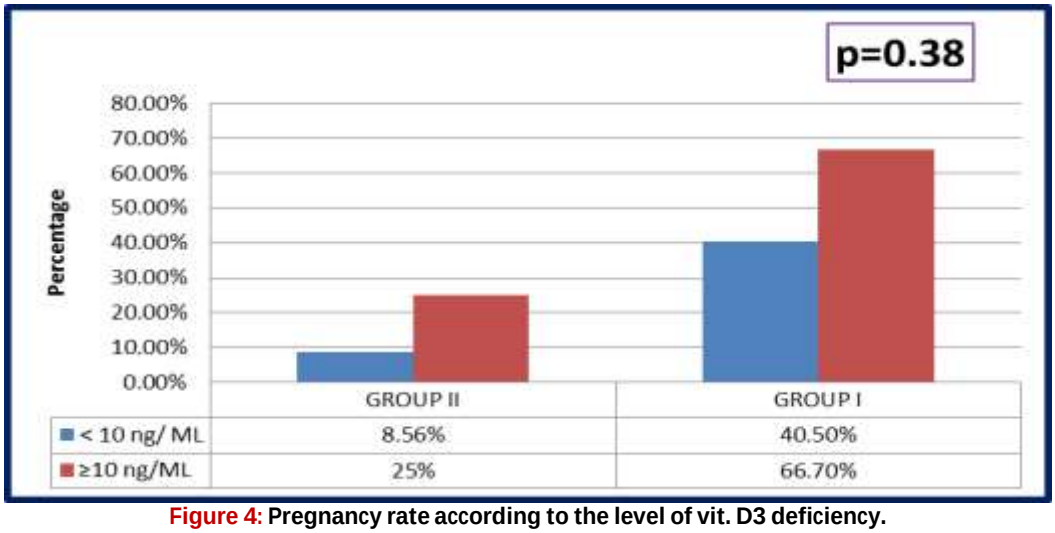

Figure 4: Pregnancy rate according to the level of vit. D3 deficiency.

*Significance (P < 0.05) Group I(patient received vit. D supplement), Group II (control).

6. Effect of Age on vit. D Level

No significance difference in between 2 groups as the p value more than 0.05 as shown in table (2).

Table 2: Difference in vit.D level according to age

Variable	Group I vit.D level	Group II (control) vit.D level
< 35 years old.	5.81±4.4	5.83±3.3
≥ 35 years old.	7.69±4.52	7.76 ± 4.223464
P value	0.124175	0.084602
Values were expressed by % or mean± standard deviation.		

DISCUSSION

Deficiency of vitamin D is common in our population, vitamin D deficiency prevalence was about 95.5% in our population. In our study the 2 groups studied had vit.D below 20ng/ml, and most of them severely deficient.

Our study show that treatment of vitamin D insufficiency increased cycle outcomes significantly in term pregnancy rate. Vitamin D mechanism affecting subfertility is far from clear. The mechanisms affecting ovarian steroidogenesis and implantation have been postulated (4). There is a suggestion by invitro study that there might be a correlations between granulosa cell function and vitamin D insufficiency (10). Vitamin D management affect antimullerian hormone (AMH) receptor II gene appearance, down-regulating FSH receptor and increasing progesterone synthesis and 3-hydroxysteroid dehydrogenase appearance. The best effect on the metabolic changes in PCOS by vitamin D expressed as a lowering in androgen levels and insulin resistance have been lead to a healthy ovarian functional physiology (10,11). A recent studies analyse the role of vitamin D in ART outcomes. Garbedian et al. assessed the role of vitamin D on clinical pregnancy rate in IVF. They found female with sufficient concentration (more than 30 ng/ml) of serum vitamin D have significantly clinical pregnancy (4).

Pregnancy rates decreased with decline of vitamin D levels. Vitamin D level was oppositely correlated to pregnancy outcomes. There were statistically significant correlation between race effect on vitamin D and clinical pregnancy (7) found significant relationship between serum vitamin D levels and implantation rates, clinical pregnancy rates, and live birth rates. In a second study (12), the same authors study serum vitamin D level between oocyte donation recipients, observed a positive correlation between clinical pregnancy rate and vitamin D level and proposing the particular role of vitamin D concentration to be through the effect on endometrial receptivity instead off embryo quality or ovarian stimulation, so we should confirm that similarly both early pregnant endometrium and cyclic endometrium considered as an extra-renal vitamin D production site ; furthermore, the impact of vitamin D at the uterus is believed to be effect through the receptors of vitamin D (VDR) via the hormonal impact or control of target genes in the local immune reaction (13). While, Franasiak *et al.* (14), two Iranian studies observed that no correlation of vitamin D level to pregnancy rates (15).

Another explanation for our results is correlated to the impact of vitamin D in reproduction. Local synthesis of 1, 25-(OH)2 vitamin D by decidua, immune cells, and invading trophoblasts could be suggested to the maternal-fetal surface growth regulation and implantation (16).While others supposed to be a correlation among reproductive function and serum calcium concentrations and this is confirmed by VDR null mutant female mice(17).

Although there is higher pregnancy rate among younger age group but this is not significant. The exact contributors for the age-related lowering of women fertility were the decrease in the oocyte quality and uterine receptivity (18) the decrease in ovarian reserve, the primordial follicles arrest and FSH levels increasing with advancing age (19) There was no correlation between age and vitamin D status and type of infertility (20,21).

CONCLUSION

Our randomized interventional controlled trial has confirmed that vitamin D insufficiency negatively correlated with pregnancy rate, founding a new therapeutic modalities for subfertile female. Although, evidence for impact of vitamin D concentrations on fertility treatment data are still deficient and done so far may not gather all the Hill's standards for the causation.

Vitamin D deficiency prevalence was about 95.5% in our population. This is alarming high and more than the previous reports in the most of the other countries. Short sun exposure span, nutritional and clothing habits may cause this difference. Vitamin D supplementation have some useful impact on human reproduction. It is cheap and safe treatment.

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CONFLICT OF INTEREST

None

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