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The role of Vitamin D supplement to clomiphene citrate for induction of ovulation in overweight PCOS women

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Abstract

Polycystic Ovary Syndrome (PCOS) is a common endocrine illness leading to infertility in women. Clomiphene Citrate (CC) is a common medication used to induce ovulation in women with PCOS, but due to the presence of hyperinsulinemia, it can sometimes be effective, especially in overweight individuals with PCOS. Furthermore, obesity exacerbates vitamin D deficiency in women with PCOS and has been linked to insulin resistance and other PCOS symptoms. Such, the object of this study is to better understand how vitamin D supplementation can enhance ovulation induction with clomiphene citrate in overweight women with PCOS who are resistant to clomiphene citrate. In a double-blind study involving 220 PCOS patients, it was found that the pregnancy rate with vitamin D supplementation plus CC was somewhat higher (if not statistically significant). The hormonal profile and demographics of both groups were fairly similar. Complications were similar except there were more nausea and vomiting in the vitamin D group. Although further research with larger sample sizes is necessary to investigate these trends, this study suggests that vitamin D supplementation may possibly have a role in ovulation induction in overweight PCOS women. Supplementation with vitamin D could represent a potential adjunctive therapy for the treatment of PCOS; however, further research is required to definitively assess its value.

Keywords: PCOS, Vitamin D supplementation, Ovulation induction, Clomiphene citrate (CC), Overweight women, Infertility

Introduction

Polycystic ovary syndrome (PCOS) is a multi-factorial endocrine disorder prevalent in women of reproductive age and manifests as a number of symptoms including menstrual abnormalities, hyperandrogenism leading to hirsutism and acne, and anovulation resulting in infertility [1]. The most difficult aspect of having PCOS is ovulatory dysfunction, as most women with this disorder will experience difficulty discharging eggs consistently and, therefore, conceiving [2]. PCOS affects 4-12% of women worldwide at reproductive age [3] and causes 90-95% of infertility in women who are sub-fertile due to anovulation [4].

Clomiphene citrate (CC) is an anti-estrogenic drug that has typically been used to induce ovulation in women with PCOS [5], CC induces the release of the follicle-stimulating hormone (FSH), which causes the ovaries to ripen and release eggs. The efficacy of CC is highly variable in patients with PCOS [6,42].

In particular, obese women with PCOS typically face an uphill battle to the induction of ovulation and require higher CC doses and longer treatment cycles. The disorder is commonly associated with the presence of an excessive level of insulin in the blood, termed hyperinsulinemia. The excess insulin can throw off the delicate equilibrium of hormonal levels in the body and prevent CC from inducing ovulation [7].

Vitamin D (VD), a fat-soluble vitamin, has attracted a great deal of attention lately due to its many important health benefits. Although VD plays a well-established role in bone health, the discussion about its non-skeletal health benefits is still open to debate [8]. VD deficiency has become an extensive phenomenon around the world, resulting in one of the most widespread nutritional deficiencies ever documented [9].

Research indicates that VD deficiency rates are disproportionally higher among women with polycystic ovary syndrome (PCOS) compared to the general adult population, which have rates that range from 20% to 48% [10] and typically greater than 80% in the majority of studies [11, 12, 13]. In women with PCOS and a high body mass index (BMI), the deficiency is worsened further. The fat value of VD affects its effective and availability in the body since it is laid down in fat [14].

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The increasing prevalence of obesity in women with PCOS and thus possible treatment options for improved ovulatory stimulation and chances for successful conception make the case for certain adjunct therapy, including vitamin D, reasonable [15]. Evidence of the link between vitamin D levels and PCOS characteristics like infertility, insulin resistance, and hirsutism is building from several research studies [16].

Vitamin D can also impact gene transcription and hormonal pathways and may influence fertility and women's insulin metabolism [17]. Additionally, and potentially relevant to the overall study, there is evidence that 1,25(OH)2D3 as a vitamin D derivative upregulated the expression of HOXA10, a master regulator of endometrial development, in endometrial stromal cells from women's endometrium. Overall, it is concluded that vitamin D3 supplementation with adequate calcium intake might regulate menstrual cycles and/or ovulation reversal by promoting oocyte maturation and activation [18,41].

Furthermore, vitamin D has also demonstrated to reduce abnormally high serum anti-Müllerian hormone (AMH) in PCOS patients [19]. Excessive serum AMH is associated with follicular arrest and decreases antral follicle sensitivity to follicle-stimulating hormone (FSH) and, therefore, the antral follicles with ovulatory potential [20].

Numerous studies have been published which demonstrated an inverse relationship between vitamin D status, hyperandrogenism (hyperandrogenemia) and insulin resistance in women with PCOS. Vitamin D replacement at high-dose weekly doses as high as 50,000 to 60,000 IU have shown to have benefits in women with PCOS regarding improvement in hyperinsulinemia, improvements in androgen-related symptoms as well as positive impact on fertility outcome measures [21].

The goal of this study is to measure the effects of vitamin D supplementation on ovulation induction in women with PCOS with the clomiphene citrate resistant condition. The study will add to the understanding of vitamin D supplementation and its effect on improving the efficacy of ovulation induction therapies by exploring its potential in this subgroup of women with PCOS.

Methods

Study design and setting

A double-blind study was conducted at the Infertility Clinic of AL-Batool Maternity Hospital between May 2020 and August 2021.

Participants

The study population consisted of 220 women with a diagnosis of polycystic ovary syndrome (PCOS) based on ultrasound features, hyperandrogenism, and oligomenorrhea [22]. The subjects' age range was between 18 and 38 years, and their body mass indices (BMIs) were between 25 and 35 kg/m2. Each subject was Clomiphene citrate resistant and failed to ovulate after three months of treatment at a daily dose of 150 mg given for five days.

Inclusion and exclusion criteria

All participants had a thorough history assessment including age, marital status, occupation, and relevant medical history such as prior pelvic surgery or medical diagnoses. Clinical assessments were carried out, after which FSH and AMH hormone levels were obtained in the laboratory. Ultrasonography was then performed to rule out uterine anomalies, abnormal male sperm analysis on the basis of WHO 2010 criteria,)23), tubal factors, endometritis, premature ovarian failure, hyperprolactinemia disorders, and any existing or recently stated vitamin D treatment.

Intervention

Participants were instructed to take 10,000 IU (Nutrocare, Winzor) twice a week for three months [24]. This intervention was followed by Clomiphene citrate (Clomid® 50 mg tablet, Sanofi Aventis), which was given at the daily dose of 150 mg for 5 days. Then on cycle day 9, regular follow-ups were organized with ultrasonography for folliculometry. The follow-ups were done bi-daily for 3 cycles until either a dominant follicle had been observed (18 ml in diameter) or day 21 of the menstrual cycle. When a dominant follicle was noted, participants received HCG 10,000 IU IM (Choriomon IU, IBSA). Timed intercourse was to occur 36 -48 hours after the HCG injection. Outcomes of pregnancy were made using B-

HCG tests two weeks after the HCG trigger [25]. The flowchart for selecting patients is shown in Fig 1.

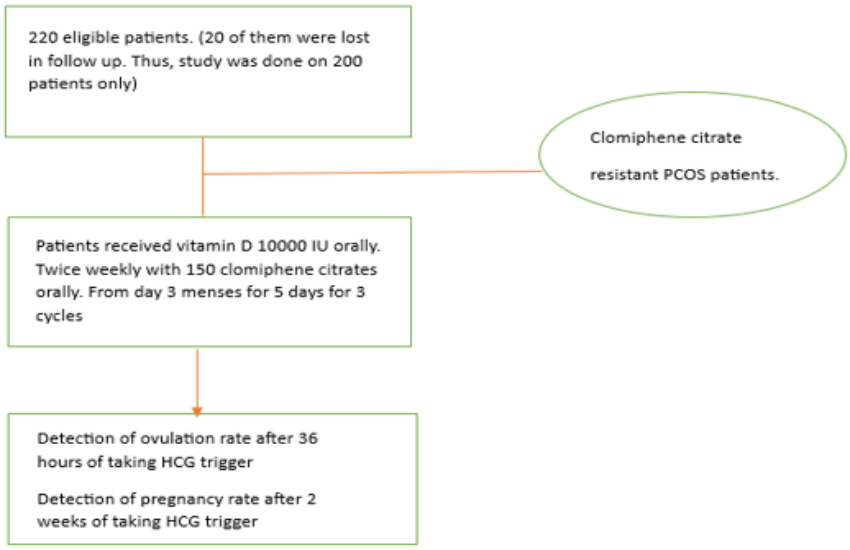

Fig. 1. Flowchart of patient's selection

Data Analysis

The collected data was presented as mean, standard deviation, or in percentages. P-value was used to calculate statistical significance.

Results

Demographic and clinical characteristics

The basic demographic and clinical features (Group I and Group II) are compared in Table 1. The age distribution of the members of Group I was 27.47 ± 5.07 years, with a range of 20 to 39 years. On the other hand, Group II's mean age was 26.35 ± 4.2 years, with ages ranging from 20 to 34. With a p-value of 0.231, statistical analysis revealed no significant difference in the age distribution between the two groups, categorizing it as non-significant (NS).

An additional variable being considered is the Body Mass Index (BMI). The BMI values in Group I varied from 28 to 39 kg/m^2, with an average of 34.5 ± 2.7 kg/m^2. With a mean of 35.85 ± 2.6 kg/m^2, Group II's BMI I ranged from 30 to 42 kg/m^2. With a p-value of 0.155, the difference in the BMI averages between the two groups was similarly determined to be non-significant.

Statistical analysis revealed a non-significant difference (p-value of 0.658) between the two groups, corroborating our findings. In particular, the marriage durations of the cases in Group I ranged from 2 to 6.2 years, with an average of 3.8 ± 1.0 years. Similar to Group I, cases in Group II had marriages lasting 2.5–7 years on average, with a mean of 4 ± 1.1 years.

Additionally, the infertility period was evaluated. Group I saw an average duration of 2.7 ± 0.99 years, ranging from 1 to 5 years. Group II experienced a mean duration of 2.48 ± 1.10 years over a period ranging from 1 to 6 years. A p-value of 0.401 suggests no statistically significant difference in the infertility period between the two groups.

Lastly, there were two categories for infertility: primary and secondary. Of the cases in Group I, 42% had secondary infertility, and 58% (58 out of 100) had primary infertility. Group II, on the other hand, had a marginally higher percentage of cases of primary infertility (66%) and secondary infertility (34%). Based on statistical analysis, Group II's primary infertility distribution was found to be significantly different, with a p-value of 0.02. P-values of 0.748 and 0.519, respectively, show that there was no significant difference between the two groups when comparing primary and secondary infertility.

Table 1. Basic demographic and clinical characteristics

Variable	Group I (n = 90)	Group II (n = 90)	P-value
Age (Years): Range Mean±S.D	 20-39 27.47±5.07	 20-34 26.35±4.2	 0.231 (NS)
BMI (Kg/m^2): Range Mean±S.D	 28-39 34.5±2.7	 30-42 35.85±2.6	 0.155 (NS)
Marriage duration (Years): Range Mean±S.D	 2-6.2 3.8±1.0	 2.5-7 4±1.1	 0.658 (NS)

Hormonal and biochemical profile

The hormonal and biochemical profiles of the two groups—the cases and the controls—are shown in Table 2. Serum FSH levels were measured for both groups, and results showed no statistically significant difference (P = 0.205), with cases reporting an average of 6.34±1.7 mIU and controls at 5.62±1.5 mIU. Similar findings were noted for serum LH levels, with cases averaging 13±2.5 mIU and controls 12.65±3.1 mIU, resulting in a non-significant p-value of 0.361. There was a slight variation in the LH/FSH ratio between the two groups (P1 = 0.315), with the average values for cases and controls being 2.2±0.3 and 2.48±0.53, respectively.

The average free serum testosterone levels in the cases were 3.66±0.5 Pg/ml, marginally higher than the average of 3.24±1 Pg/ml in the controls. However, P = 0.312 indicates that the difference was not statistically significant. Average serum prolactin levels for cases were 10.75±3.6 ng/ml, while controls had an average of 10±2.3 ng/ml. This difference was not statistically significant (P = 0.218). The serum progesterone levels for the cases and controls were 15.86±3.2 and 13.22±4 ng/ml, respectively, with no significant difference observed (P = 0.342). The average serum estradiol levels in the cases were 325±32 Pg/ml, whereas the controls had 389±35 Pg/ml. There was no significant difference between the two groups (P = 0.122).

Serum estradiol levels in the cases averaged 320±54 Pg/ml at ovulation, while the controls averaged 201-382 Pg/ml. Interestingly, Group I's estradiol levels were noticeably higher than group II's (P = 0.012). There was no statistically significant difference between the two groups (P = 0.178) regarding fasting blood sugar (FBS), with the cases' average being 108±22 mg/dL and the controls' varying from 70-167 mg/dL.

Table2. Hormonal and biochemical profile of both groups

Variable	Group I n = 100	Group II n = 100	P-value
Serum FSH (mIU) Range Mean±S.D	 3.5-9 6.34±1.7	 3.2-9.1 5.62±1.5	 0.205 (NS)
Serum LH (mIU) Range Mean±S.D	 6.2-18 13±2.5	 6.1-20 12.65±3.1	 0.361 (NS)
LH/FSH Ratio Range Mean±S.D	 1.7-3.1 2.2±0.3	 1.86-4.1 2.48±0.53	 0.315 (NS)
Free Serum Testosterone (Pg/ml) Range Mean±S.D	 2.54-3.8 3.66±0.5	 0.7-8 3.24±1	 0.312 (NS)
Serum Prolactin (ng/ml) Range Mean±S.D	 2.15-20 10.75±3.6	 6.14-21.5 10±2.3	 0.218 (NS)
Serum Progesterone (ng/ml)			

Range Mean±S.D	9.12-23 15.86±3.2	8.11-30 13.22±4	0.342 (NS)
Serum Estradiol (Pg/ml) Range Mean±S.D	 257-390 325±32	 217-375 389±35	 0.122 (NS)
Serum Estradiol at time of ovulation (Pg/ml) Range Mean±S.D	 215-390 320±54	 201-372 288±51	 0.012 (S)

Folliculometry and ovulation outcome

Follicle size was measured using folliculometry on the twelfth day of the previous cycle. The mature follicles in the cases group had an average size of 17±3.1 mm, ranging from 11 to 21 mm. In contrast, the average measurement in the control group was 16±2.9 mm, with a range of sizes between 11 and 20 mm. Significantly, Table 3 shows that the difference between the two groups was not statistically significant at induction, with a P-value of 0.518.

Regarding ovulation and pregnancy outcomes, 50 out of 100 cases (or 50%) had a successful ovulation and subsequent pregnancy. By contrast, 40 out of 100 controls, or 40% of the Group, had the same result. As shown in Table 3, the statistical analysis revealed that although there appeared to be a rise in ovulation and pregnancy success in the cases group, this rise wasn't significant. Visual representations of the ultrasound results about the patient's ovaries and follicle sizes are shown in Figs. 2 and 3.

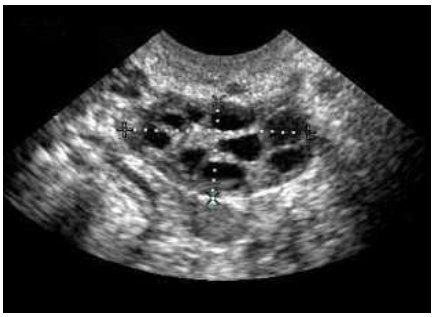

Fig. 2. U/S of a PCOS patient showing multiple cysts in the ovary of the affected woman

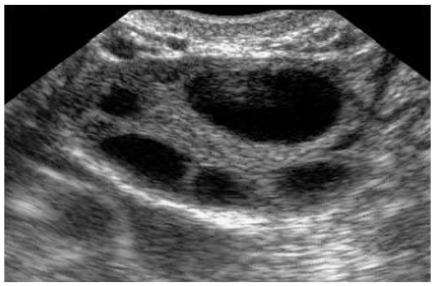

Fig. 3. U/S Flouculometery of a PCOS patient viewing that the largest diameter of the largest follicle is 18 mm after the therapy.

Follow-up complications

Both groups showcased similar post-treatment complications. However, a noteworthy distinction was observed in nausea and vomiting. The cases group demonstrated a significantly higher incidence of these symptoms, as confirmed by a p-value of 0.021, elaborated further in Table 4.

Table 4. Follow-up complications occurrence in patients of both groups.

Variable	**Group I n (%)**	**Group II n (%)**	**P-value**
Headache	3 (3%)	5 (5%)	0.231 (NS)
Nausea and Vomiting	8 (8%)	3 (3%)	0.021 (S)
Breast Tenderness	3 (3%)	2 (2%)	0.758 (NS)
Abdominal Distention	4 (4%)	6 (6%)	0.231 (NS)
Visual Disturbances	3 (3%)	3 (3%)	1.00 (NS)
Ovarian Hyperstimulation Syndrome (OHSS)	2 (2%)	3 (3%)	0.758 (NS)
P-value	0.254 (NS)	0.317 (S)	

Discussion

Polycystic ovarian syndrome (PCOS) is a prevalent disorder for women of reproductive age affecting 6-10% of this population [5,26]. In fact, 70-80% of reproductive impairment (i.e., infertility or subfertility) is due to anovulatory cycles secondary to PCOS [27]. Although productive medications exist to induce ovulation in women diagnosed with PCOS, many still have difficulty establishing a pregnancy. Also, alterations in endometrial receptivity are positively associated with an increased risk of miscarriage [24, 27].

Clomiphene citrate is a selective estrogen receptor modulator, and this first-line oral medication is recommended for patients with PCOS to induce ovulation with a success rate of 78-85%. [28, 29] In the present study, one hundred eighty women who were diagnosed with PCOS from private infertility clinics participated in the study. The mean ages of the cases and controls were 26.35 and 27.47 years, respectively. There was no significant difference in age, which is consistent with the reports by Li et al. [25] and the data reported by Akpinar et al. [28].

The study found no difference in anthropometry (weight, height, and BMI) across the groups, which support Li et al. [25]. Conversely, Jamilian et al. reported a significant increase in BMI for patients without vitamin D supplements [27,40]. Similarly, the present study agree with the report of Yahya et al. [30] with respect to the BMI.

The results were also consistent with studies conducted by Jamilian et al., Akpinar et al., Ibrahim et al., and Yahya et al. regarding the duration of infertility; none of the studies reported any significant differences between the study groups examined [27, 28, 29, 30]. Moreover, the results coincides with studies by Li et al. and Akpinar et al., who also found no significant differences in the type or duration of infertility [25, 28].

There was no conclusive dominant type of infertility; however the researchers did find that secondary infertility was more frequent in the control group. These results are similar to the results reported by Akpinar et al. [28]. Hormonal markers such as LH, FSH, and LH/FSH ratio did not show any significant change between groups. Whereas Yuan et al. and Chen et al. observed significant decreases in serum levels of LH and FSH in their groups [31, 32], the present results were consistent with Li et al. and Yahya et al. [25, 30].

Unlike the results of Sirmans et al., which show an association between PCOS and diabetes mellitus, neither of the fasting blood sugar levels in the study differed significantly between groups [33]. Yahya et al., found results similar to the results of the current study, while Jamilian et al., noted a significant increase in fasting blood sugar in the groups that did not take vitamin D supplements [27].

Yahya et al. [30] observed significant differences in serum testosterone level values were found in both groups. The differences in serum progesterone levels, however, are not consistent with the findings of Deng et al. [34] who showed significant increases in serum progesterone values following PCOS treatment. The serum estradiol levels findings are in agreement with the findings of Yuan et al. and Chen et al. [31, 32].

The study departs from the conclusions drawn by Jamal et al. and Morin-Papunen et al. related to BMI, as both support weight loss as the most relevant therapeutic intervention for obesity in women with PCOS with regard to infertility [35,36]. The study results in line with the outcomes of Pourali et al. and Yahya et al. [30,37] regarding follicular size, stimulation outcomes and ovulation induction. Finally, while this is not statistically significant, the greater success at inducing pregnancy in one of the groups is supportive of the findings from Brown et al. [38] and Rasheed et al. [39].

Although Cunha and Povoa [5] interpret vitamin D supplementation as a possible therapeutic 'auxiliary' agent in treating ovulation dysfunction and metabolic dysfunction in women with PCOS, the study is consistent with the findings of Yahya, et al., and should be interpreted as indicating there is no real difference in the pregnancy success outcomes between the cohorts [30].

Conclusion

In conclusion, this investigation evaluated the effect of supplementation with vitamin D on outcomes in overweight women with resistant ovulation and PCOS who were being treated with clomiphene

citrate (CC). The combination resulted in a somewhat improved pregnancy rate in the vitamin D group, even though there were no statistically significant differences. The two groups closely resembled each other with respect to hormonal variables, clinical characteristics, and demographic factors. The two groups had closely similar measures of mature follicle size, ovulation, and pregnancy outcome, with the vitamin D group having a non-substantial improved success rate. Apart from increased nausea and vomiting in the vitamin D group, the complications were largely similar across groups. The study concluded that while inconclusive, vitamin D supplementation may play a role in the process of ovulation induction for overweight women with PCOS. More research, with larger cohorts, is required to validate these effects, but vitamin D supplementation as part of PCOS management may provide an adequate interim approach.

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Ethics approval and consent to participate:

The study was ethical, scientific approval from scientific community in the Department of Obstetrics and Gynecology, College of Medicine, University of Diyala, Iraq, and also approval of the Infertility Clinic of Al-Batool Maternity Hospital following the permission from the Ministry of Health. All the processes were carried out according to ethical and legal requirements.

Consent for Publication:

Publication approval was granted by the scientific community in the Department of Obstetrics and Gynecology, College of Medicine, University of Diyala.

Availability of Data and Materials:

All relevant data supporting the findings of this study are included in the manuscript. Additional data may be available from the corresponding author upon reasonable request.

Competing Interests:

The authors declare no competing interests.

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Authors' Contributions:

Raakad Kamel Saadi, Enas Jaleel Alobaidy, and Azhar Imran Ibrahim were responsible for the study's conception, design, data collection, analysis, and manuscript preparation.

Code Availability:

Not applicable.

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