ORIGINAL ARTICLE

CONTENTS

The efficacy and safety of vitamin D supplementation in women with polycystic ovarian syndrome undergoing ovulation induction using letrozole

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ABSTRACT

Aim: To examine the role of vitamin D supplementation in PCOS women who failed to ovulation induction by letrozole in previous trials.

Materials and Methods: The study included 30 women diagnosed with PCOS and were complaining from primary infertility. Those women had previously been treated for 3 months with letrozole to induce ovulation, but there was failure of response to treatment. Those 30 women were selected from a pool of women who were evaluated for serum vitamin D and were proved to have vitamin D deficiency (<20 ng/ml).

Results: Daily monitoring of ovulation by transvaginal ultrasound was done staring from day 7 till day 25 of the cycle. The main outcomes were the number and the size of follicles. In addition, they were followed up for evidence of pregnancy using biochemical serum and urine examination.

Conclusions: When women with polycystic ovarian syndrome are treated with letrozole, vitamin D supplementation enhances both the result of ovulation induction and pregnancy.

KEY WORDS: polycystic ovary syndrome, ovulation, vitamin D

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INTRODUCTION

Infertility is a common health problem in our community [1-3]. Despite the large number of articles published annually about infertility in Iraq, there is no large national population-based study to figure out the exact prevalence of infertility in Iraq population. However, the prevalence rate of infertility globally is in the range of 8% to 12% [4]. The causes of infertility are variable, but they can be grouped into 4 major categories and these are male factors, female factors, combined factors and unexplained infertility category [5]. Female infertility can be due to variety of causes affecting the structure and function of reproductive tract [6]. One of the most prevalent reasons for female infertility is polycystic ovarian syndrome [7]. It is the most common women endocrine abnormality [8]. It is characterized by anovulation, menstrual irregularities, hyperandrogenism based on clinical and biochemical evidences, and polycystic ovary based on imaging techniques, ultrasound examination in particular [9]. The disease is also associated with obesity and features of metabolic syndrome such as insulin resistance and hypertension [10]. The problem of infertility is common in women with PCOS and in a substantial proportion of them being the first cause of presentation and seeking medical advice [11]. Anovulatory infertility is a frequent side effect of PCOS, and women who experience anovulatory infertility are more likely to develop the condition (70% to 80% of the time). As a result, addressing anovulation is the main focus of the reproductive treatments provided to these women [12]. Infertility may be negatively impacted by PCOS in a number of ways, including anovulation or irregular ovulation; a higher risk of spontaneous abortion; decreased oocyte quality; insulin resistance leading to hyperinsulinemia and an increased risk of miscarriage; and long-term intimal hyperplasia that compromises implantation [13]. PCOS is believed to be caused by a vicious cycle in which excess testosterone stimulates visceral and abdominal adipose tissue depositing, insulin resistance (IR), and compensatory hyperinsulinemia, which in turn stimulates the production of androgen by the adrenal glands and ovaries. In conjunction with hypothalamic-pituitary dysfunction, this cyclical pathogenetic interplay between IR, hyperinsulinemia, and hyperandrogenism causes further ovarian dysfunction, which can cause anovulation and infertility [14]. The first-line therapy advised for PCOS-afflicted women is lifestyle modifications that encourage weight loss [15].

Ovulation induction is the cornerstone of treatment for PCOS-related infertility in women because 70% of these women experience anovulation or oligo-ovulation. The most often employed substance is clomiphene citrate [16]. Letrozole, an aromatase inhibitor, was used as an ovulation inducer in women with anovulatory infertility who had endometrial thickness greater than 6 mm. It has also been reported that letrozole is effective in patients who are resistant to clomiphene, and that it also caused ovulation in 62% of cases and pregnancy in 14.7% of cases [17]. However, sufficient controversy existed in available published articles about the efficacy of ovulation induction alone in treating PCOS infertility that justified the search for other medical forms of intervention to treat the resistant cases [18]. Vitamin D deficiency affects PCOS patients, specially those with heavy weight. A low level of vitamin D is linked to insulin resistance and an increased chance of developing diabetes, and hypovitaminosis is a risk factor for glucose intolerance [19]. Therefore, the current study was planned and conducted aiming at exploring the role of vitamin D supplementation in PCOS women who failed to ovulation induction by letrozole in previous trials.

AIM

The current study was planned and conducted to examine the role of vitamin D supplementation in PCOS women who failed to ovulation induction by letrozole in previous trials.

MATERIALS AND METHODS

STUDY DESIGN

The current interventional study (uncontrolled clinical trial) was carried out in the department of Obesteric and Gynecology at Adiwaniyah Maternity and Pediatric Teaching Hospital, Adiwaniyah Province, Iraq during the period from March 2022 till March 2023.

INCLUSION CRITERIA

Women diagnosed with PCOS according to the Rotterdam criteria; the body mass index, which falls between 18 and 35 kg/m^2.

EXCLUSION CRITERIA

Exclusion of other associated causes of infertility such as tubal blockage. Pregnant PCOS women and women with hypersensitivity letrozole were also excluded from the study.

WOMEN ENROLLMENT IN THIS STUDY

The study included 30 women diagnosed with PCOS and were complaining from primary infertility. Those women were treated previously for 3 months with letrozole to induce ovulation, but there was failure of response to treatment. Those 30 women were selected from a pool of women who were evaluated for serum vitamin D and were proved to have vitamin D deficiency <20 ng/ml.

INTERVENTION

For six months, a daily dose of 4,000 IU of vitamin D3 was administered to each of the thirty women who were selected. In addition, a course of letrozole at a dose of 2.5 mg/day at days 3-5 of the cycle for three successive months was given as an ovulation inducing agent.

FOLLOW-UP AND OUTCOME ASSESSMENT

Daily monitory for ovulation by transvaginal ultrasound was done starting from day 7 till day 25 of the cycle. The main outcomes were the number and the size of follicles. In addition, they were followed-up for evidence of pregnancy using biochemical serum and urine examination.

ETHICAL CONSIDERATIONS

The College of Medicine, University of Al-Qadisiyah's ethical approval committee granted the trial ethical approval. All enrolled women provided written consent following a thorough explanation of the current trial's methods and objectives. Formal agreements were acquired from the Iraqi Ministry of Health's official representative, the Directorate of Health.

STATISTICAL ANALYSIS

Data were transformed into an SPSS spread sheet (version 16) for purpose of statistical description and analysis. Categorical variables were expressed as percentage and number. Quantitative data were expressed as range, standard deviation, mean, median and inter-quartile range. Comparison of means was done using student t-test. Comparison of proportions was done using chi-square test. The level of significance was set at $p \leq 0.05$.

RESULTS

At the end of the study, 17 women showed positive pregnancy test and 13 women showed negative pregnancy test, thus the rate of biochemical pregnancy was 56.7% (Fig.1).

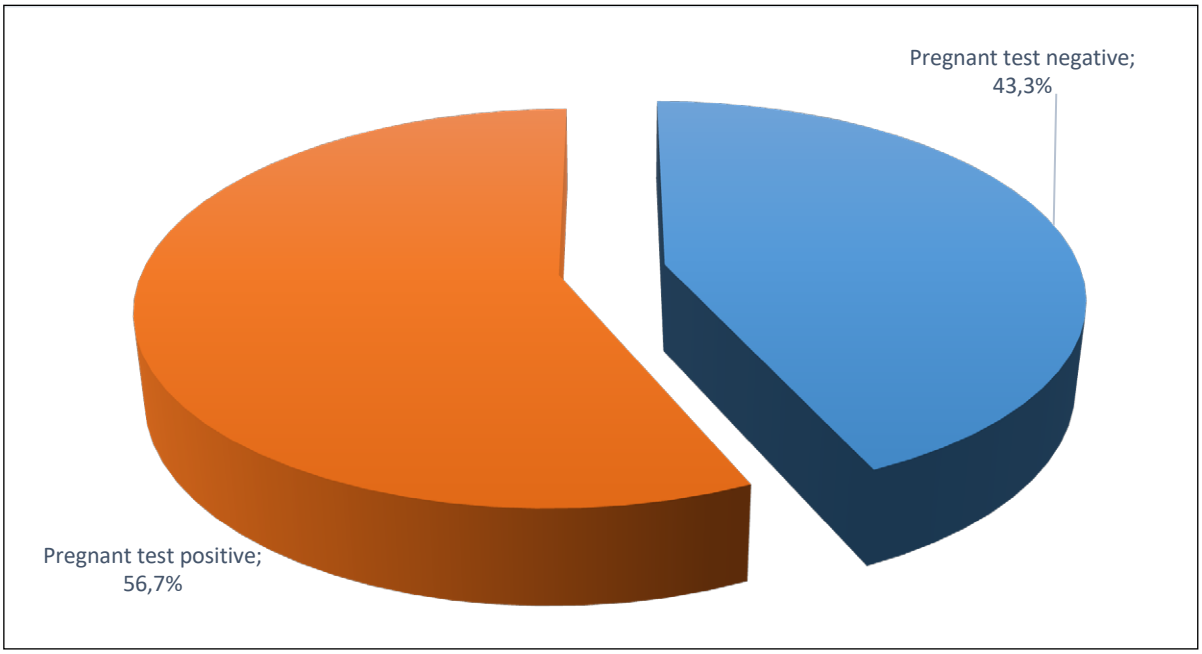

Fig. 1. Pregnancy test results among PCOS women at the end of the study.

Table 1. Comparison of characteristics of PCOS women with positive pregnancy test with those with negative pregnancy test

Characteristic		Pregnancy test positive n = 17	Pregnancy test negative n = 13	p
Age (years)				
Mean ±SD		24.05 ± 3.02	23.93 ± 4.12	> 0.05 NS
Range		20-35	19-35	
BMI (kg/m²)				
Mean ±SD		27.13 ± 7.11	29.02 ± 8.07	< 0.05 S
Range		20-35	19-35	
Duration of infertility				
Mean ±SD		2.15 ± 1.01	2.31 ± 0.92	> 0.05 NS
Range		2-5	2-5	
Size of follicles (mm)				
Mean ±SD		17.24 ± 3.05	9.02 ± 6.21	< 0.05 S
Range		15-19	7-18	
Number of follicles (>15 mm)				
Mean ±SD		4.01 ± 1.09	2.03 ± 0.97	< 0.05 S
Range		3-7	1-6	
Structure of follicles by size	<3 mm	0 (0.0%)	9 (69.2%)	
	3-5 mm	10 (58.8%)	4 (30.8%)	
	>5 mm	7 (41.2%)	0 (0.0%)	

n: number of cases; SD: standard deviation; BMI: body mass index; NS: not significant; S: significant

The rest of results will be outlined so that characteristic of pregnant women will be contrasted to those of non-pregnant women. The mean age of pregnant and non-pregnant women did not significantly differ from one another, 24.05 ± 3.02 versus 23.93 ± 4.12 years, respectively p>0.05. However, there was significant difference in mean body mass index (BMI) between pregnant and non-pregnant women 27.13 ± 7.11 kg/m^2 versus 29.02 ± 8.07 kg/m^2, respectively p<0.05; being lower in pregnant women. Between pregnant and non-pregnant women, there was no significant difference in the mean period of infertility 2.15 ± 1.01 years versus 2.31 ± 0.92 years, respectively p>0.05. There was significant difference in mean size of follicles between pregnant

and non-pregnant women 17.24 ± 3.05 mm versus 9.02 ± 6.21 mm, respectively p<0.05; the size being greater in pregnant women. In addition, there was significant difference in mean number of follicles >15 mm in diameter between pregnant and non-pregnant women 4.01 ± 1.09 versus 2.03 ± 0.97, respectively p<0.05; the number being greater in pregnant women. Moreover, it was observed that none of women with positive pregnancy had follicle number >15 mm in diameter of less than 3 and on the contrary, most of women with failure of pregnancy had mostly < than 3 follicles of the size greater than 15 mm (Table 1).

DISCUSSION

The problem of infertility is the main problem facing women with PCOS in our community and the success of getting pregnant by PCOS women has dramatic impact on improving the quality of life of these women. Therefore, the medical research trying to solve this health issue in such women is of great importance. The main problem in PCOS is anovulation, thus the use of ovulation induction by medical ways is a corner stone approach in treating infertility in PCOS women. The drug of choice in this regard is clomiphene citrate; however, in substantial number of PCOS women, this approach was proved to be unsatisfactory. Therefore, it is increasingly recommended to use letrozole as a method of inducing ovulation; and yet, the results are also not so promising. It has been demonstrated that a lack of vitamin D is linked to a number of health issues. Numerous investigations have demonstrated a connection between chronic disorders such autoimmune diseases, endocrinological or tumorous states, and vitamin D insufficiency [20, 21]. Additionally, appropriate vitamin D intake has been suggested to help these patients feel better [22]. On several levels, vitamin D interacts with the epigenome, which controls around 3% of the human genome [23]. This vitamin insufficiency is prevalent in PCOS women, and vitamin D status in PCOS is associated with reproductive function, metabolic changes, and mental health [24]. The need for vitamin D is increased by obesity, PCOS, and pregnancy ϕτв as a result, vitamin D deficiency is more prevalent and severe in people with these disorders than in healthy people [25, 26]. We suggested that the vitamin D may have a role in potentiating the effect of ovulation induction by improving ovarian response by still unknown mechanism, thus we planned the current interventional study aiming at supplementing a sample of PCOS women, who previously failed to respond to letrozole, with vitamin D and combine this approach with another cycle of ovulation induction using letrozole. The results of our study pointed out to the substantial impact of vitamin D deficiency on ovulation response in women with PCOS and we found that 17 women out of 30 women succeeded to have pregnancy and that 21 women of them succeeded to have mature follicles of the size greater than 15 mm. The fact that vitamin D receptors (VDRs) are found in both male and female central and peripheral reproductive organs, tissues, and cells emphasizes the crucial significance of vitamin D related for fertility. VDRs are also discovered in the hypophysis, hypothalamus, granulosa cells, endometrial, placenta, decidua, testes, and cells involved in spermatogenesis in males [21, 27]. Some of the physiological effects of vitamin D include promoting follicular maturation and selection, follicular stimulation hormone (FSH) receptor gene expression, and the generation of the ovarian steroid hormones progesterone, estradiol, and estrone [28]. In line with our observations, vitamin D supplementation was included to IVF treatment for PCOS-afflicted women in a recent paper. Vitamin D levels strongly correlate with the likelihood of implantation and clinical pregnancy; they improve embryo quality-the number of high-quality embryos following vitamin D treatment equals that occurring in women with normal vitamin D levels. It was discovered that both implantation and the occurrence of clinical pregnancy were significantly higher in patients with normal vitamin D levels compared to those with decreased levels of vitamin D (20 ng/mL 25(OH)-vitamin D) [29].

CONCLUSIONS

Vitamin D supplementation improves ovulation induction and pregnancy outcome in women with polycystic ovarian syndrome treated with letrozole. Vitamin D levels strongly correlate with the likelihood of implantation and clinical pregnancy; they improve embryo quality-the number of high-quality embryos following vitamin D treatment equals that occurring in women with normal vitamin D levels. It was discovered that both implantation and the occurrence of clinical pregnancy were significantly higher in patients with normal vitamin D levels compared to those with decreased levels of vitamin D (20 ng/mL 25(OH)-vitamin D).

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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