Original Article

Role of Clomiphene Citrate Treatment in Subfertility Due to Polycystic Ovarian Syndrome

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Abstract

Objective: To assess the frequency of mature follicle rate as a result of clomiphene citrate treatment in subfertility due to polycystic ovarian syndrome.

Methodology: This descriptive cross-sectional study was conducted at Obstetrics and Gynecology department, CMH (Combined Military Hospital), Multan, for 6 months from 1st March to 1st September 2023. The study comprised of 373 cases aged between 20–40 years reporting infertility for longer than a year, having body mass index <28, and having subfertility owing to PCOS. All study participants were subjected to clomiphene citrate treatment. Each woman continued to receive metformin 500 mg thrice a day. Development of mature follicles was observed utilizing transvaginal ultrasound from 10th day onwards.

Results: Of 373 females the mean age of patients was 32.07±4.22 years. Mean weight of the patients was 59.54 ± 6.05 kg whereas the mean height was 1.61 ± 0.067 m. Mean body mass index (BMI) was 22.92 ± 2.28 kg/m². 203(54.4%) patients had primary while 170 (45.6%) had secondary infertility. 128(34.32%) patients had mature follicles on ultrasonography after receiving clomiphene citrate treatment.

Conclusion: It was concluded that patients receiving clomiphene citrate treatment had acceptable number of mature follicles, thereby likely increasing pregnancy rates in women with PCOS.

Keywords: Clomiphene citrate, mature follicles, subfertility, polycystic ovarian syndrome.

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Introduction

Polycystic ovarian syndrome (PCOS) is the most frequently occurring endocrine dysfunction in females, manifesting in a number of clinical patterns such as irregular menstruation, excessive androgen in terms of acne and hirsutism, and multiple small ovarian cysts. It has been widely reported in approximately 4-18% of reproductive age women all over the world.[1, 2] It is one of the common causes of infertility in reproductive age women. Although the exact pathophysiological mechanism causing PCOS is unknown, some of the clinical manifestations are thought to occur as a result of abnormal luteinizing hormone (LH) and androgens levels which hinder the normal ovarian function.[3] PCOS is generally diagnosed by the Rotterdam criteria 2003[4]. The individual must fulfill 2 of the three criteria to have confirm diagnosis of PCOS: a) oligo ovulation, anovulation, or both; b) raised androgen levels; and c) polycystic ovaries on transvaginal ultrasound.[4] Infertility in PCOS is treated by induction of ovulation which can be done either by medication or surgery.[5]

Clomiphene citrate was first introduced in 1960 for treating a type of subfertility in which hormone levels remain normal.[3] Presently, clomiphene citrate is regarded as the first-line therapy for infertility caused by PCOS.[6] It is administered orally and is comparatively safer and cheaper, however it can cause a number of side effects. It is a selective estrogen receptor modulator that creates positive estrogenic effects and antagonist role in various tissues such as endometrium, causing damaging effects.[7] Induction of ovulation

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occurs through competitive binding of clomiphene citrate to estrogen receptors in the pituitary and hypothalamus thus decreasing the signaling of estrogen via its receptors. As a result, the feedback mechanism of endogenous estrogen receptors is hindered causing an upsurge in the secretion of follicle stimulating hormone and luteinizing hormone, thereby stimulating production of ovarian follicles.[2] The dose for clomiphene citrate ranges from 50-150 mg.[8]

However, Clomiphene Citrate (CC) resistance is encountered in almost 25% of patients with infertility thus causing inability to ovulate and conceive with CC and subsequently suffer from CC failure.[9] It has also been reported to exhibit compromised efficacy consisting only a live birth rate of 22% and elevated probability of multiple pregnancies.[10] A study revealed that induction of ovulation with Clomiphene Citrate might cause lower endometrial thickness than other ovulation induction therapies.[2] A study reported that ovulation rate was 59% in patients receiving clomiphene citrate treatment.[11] Another study revealed that the rate of mature follicles production was 41.25% after clomiphene citrate treatment.[12]

The rationale of this descriptive study was to see the number of mature follicles in patients receiving clomiphene citrate in treatment of subfertility due to PCOS. As there is scarce local data available and global data gives contrasting results in terms of number of mature follicles, so the results of this study would be beneficial.

Methodology

At the Obstetrics and Gynaecology department of the Combined Military Hospital in Multan, descriptive cross-sectional research was conducted for six months, starting on March 1 and ending on September 1, 2023. Sample size of 373 was measured utilizing 95% confidence level, 5% margin of error and expected percentage of mature follicles in the group getting clomiphene citrate as 41.25%.[12] Consecutive sampling technique was utilized to gather the data.

Patients aged between 20–40 years reporting infertility for longer than a year, having body mass index <28 kg/m², subfertility owing to PCOS (absence of ovulation, symptoms of increase in androgen in the blood such as hirsuitism and acne, and the raised levels of testosterone in the blood) were included in the study.

Patients having tubal patency on hysterosalpingography, with abnormal FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), Progesterone, Estrogen, Prolactin, and Testosterone levels, Patients whose husbands had abnormal semen analysis report were excluded from the study.

Each patient who met the inclusion criteria had their data collected once the study's participants gave their informed written consent and the ethics committee of the relevant institute approved the procedure. All cases were diagnosed for subfertility and PCOS. A starting dose of 50 mg Clomiphene Citrate was given to all patients, and then increasing the dose up to 100 mg per day for 5 consecutive days commencing on the 3rd day of menstruation. Each woman continued to receive metformin 500 mg thrice a day. Transvaginal ultrasonography (TVUS) was used starting on the tenth day to monitor the development of mature follicles. The stimulation of ovulation was initiated by a subcutaneous injection of 10,000 IU of human chorionic gonadotropin (hCG) as soon as TVUS revealed the presence of at least one mature follicle with a mean diameter of at least 18 mm. The researcher gathered all of the data themself.

Version 23 of the statistical programme for social sciences (SPSS) was used to enter and analyse all of the data. Quantitative information was displayed as Mean ± Standard Deviation, including age, weight, height, and body mass index. Categorical data like type of infertility and number of mature follicles were presented as frequencies and percentages. Chi-square test was utilized to compare the number of mature follicles following clomiphene citrate treatment with respect to age, body mass index, and type of infertility.

Results

A total of 373 patients were included in the study. Baseline characteristics are explained in Table I. Mean age of patients was 32.07±4.22 years, with a range of 20 years. Mean weight of the patients was 59.54 ± 6.05 kg whereas the mean height was 1.61 ± 0.067 m. Mean body mass index (BMI) was 22.92 ± 2.28 kg/m². 203(54.4%) patients had primary while 170 (45.6%) had secondary infertility.

Figure 1 illustrated the Number of Mature Follicles in patients receiving clomiphene citrate for the treatment of subfertility due to polycystic ovarian syndrome. 128(34.32%) patients had mature follicles on

ultrasonography after receiving clomiphene citrate treatment.

Table I: Baseline parameters of patients having subfertility due to PCOS. (N=373)		
Age* (years)	32.07±4.22	
Weight* (kg)	59.54 ± 6.05	
Height* (m)	1.61 ± 0.067	
BMI* (kg/m²)	22.92 ± 2.28	
PARAMETERS	**N**	**%**
Type of infertility		
Primary	203	54.4
Secondary	170	45.6

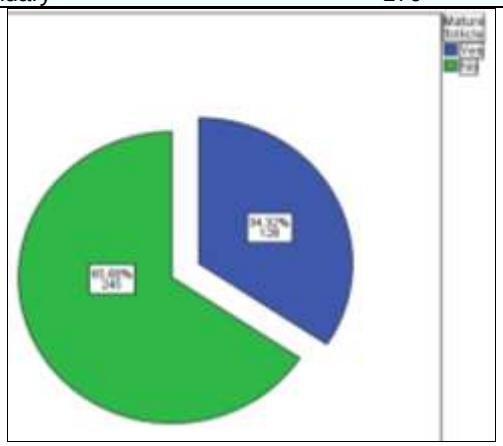

Figure 1. Number of Mature Follicles in patients receiving clomiphene citrate for the treatment of subfertility due to polycystic ovarian syndrome.

Table II showed the comparison of mature follicle rate following administration of clomiphene citrate with respect to age, body mass index, and type of infertility. Results demonstrated that patients who belonged to 20-30 years age group responded better to clomiphene citrate in terms of follicular maturation (p = 0.000). Whereas, there was no statistically significant difference between normal weight and overweight individuals regarding number of mature follicles following clomiphene citrate treatment (p = 0.860).

Discussion

For females experiencing infertility as a result of polycystic ovarian syndrome, safe and efficient ovulation induction is essential.[13] For females with PCOS, clomiphene citrate is thought to be the first-line treatment drug for inducing ovulation. Clomiphene citrate dosage recommendations range from 50 mg to 100 mg daily, with a maximum of 250 mg. Nonetheless, clomiphene resistance is widespread, seen in 15% to 40% of PCOS-affected women.[14] In this cross-sectional study, 373 female cases reporting subfertility were included. All patients received clomiphene citrate to induce ovarian follicle maturation.

Table II: Comparison of mature follicle rate following administration of clomiphene citrate with respect to age, body mass index, and type of infertility. (N = 373)				
Factors	**Mature follicle**			**p-value***
	Yes	**No**	**Total**	
Age (years)				
20 – 30	98	55	153	
31 – 40	30	190	220	0.000
Total	128	245	373	
BMI (kg/m²)				
Normal weight	103	199	302	
Over weight	25	46	71	0.860
Total	128	245	373	
Type of infertility				
Primary	70	133	203	
Secondary	58	112	170	0.941
Total	128	245	373	

In the present study, 34.32% patients had mature follicular development as a result of clomiphene citrate treatment. It is comparable to the results of various other studies.[6, 15-19] A study conducted by Shafiq et al. showed that frequency of ovulation in sub-fertile females with PCOS was 42.28%. A study reported that Efficacy of CC was only 10.38%.[19] In another study conducted by Hegde et al., it was reported that monofollicular development was 61.9% in patients receiving CC. [20]

Ashfaq et al. reported that clomiphene showed effectiveness in just 32.4% women.[21] In a literature review carried out by Kailey Potratz, higher ovulation and pregnancy rates, and greater live birth rates were reported after Letrozole therapy, as compared to CC.[22] Zaman et al. reported that the successful ovulation was achieved in 56% in patients taking CC.[23] 85.2% was the cumulative ovulation rate with CC, as reported by Bansal et al. [13] In a study carried out by Badawy et al., compare the impact of early and late luteal phase administration of CC in PCOS, it was reported that ovulation occurred more in early CC group as compared to the late group (59.1% vs. 51.9%). Number of mature follicles was also higher in early CC group.[24]

Another study revealed that the ovulation rate using CC in anovulatory women is about 70–85%, but only about one half conceive with the pregnancy rate of 36% and live-birth rate of 29% per patient.[25] One more study by Al-Shaikh et al. reported that as a result of treatment with CC, one, two and three mature follicles had developed in (87.87%), (9.67%) and (3.22%) cycles, respectively.[26] According to a research by Sharma et al., the number of mature follicles was considerably greater in the clomiphene group ($p<0.05$) when tamoxifen and clomiphene citrate were compared for

effectiveness. Ovulation rates, however, were comparable across the two groups (66.6% vs. 70%, p=0.715).[27]

Conclusion

It was concluded that patients receiving clomiphene citrate treatment had acceptable number of mature follicles, thereby likely increasing pregnancy rates in women with PCOS.

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