Original Research Article

Clinical study of ovulation induction with clomiphene citrate in infertility patients with polycystic ovary syndrome

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Abstract

Background: Normogonadotrophic anovulation, is the most common category of anovulatory infertility. Within this group, polycystic ovary syndrome (PCOS) is by far the most prevalent cause, accounts for 85% of anovulatory females. With increasing modernization, its prevalence is growing rapidly. Induction of ovulation in PCOS women is a challenge and the best ovulation induction drug is still debatable. In present study we assessed effectiveness of clomiphene citrate for ovulation induction and pregnancy rates in infertile women with polycystic ovary syndrome. **Material and Methods:** Present study was a prospective, observational study conducted in Women with primary/secondary infertility, with PCOS , willing to participate and follow up. Diagnosis of PCOS was made on Rotterdam criteria. Primary outcome measures are ovulation rate, endometrial thickness, mono Vs. multifollicular rate, and days to ovulation, pregnancy rate. Statistical analysis was done using descriptive statistics. **Results:** Initially 70 patients were recruited in present study. 64 patients either conceived or taken treatment for complete 6 months were considered for present study. Most common age group was 21-25 years. Mean age of study patients was 26.1 ± 3.3 years. 55% patients had normal BMI while 34 % were overweight. 77% patients had primary infertility. 73% patients had 1-5 years duration of infertility. 30% patients had history of laparoscopic ovarian drilling. Hirsutism was noted in 58%. After serial USG examinations, at the end of study monofollicular development (55%) was more common than multifollicular development (45 %). Mean endometrial thickness was 7.82± 2.29 mm. Average days for ovulation with clomiphene citrate were 14.6 ± 3.94. On day 21, average P4 values were 11.15 ± 6.81 ng/ml. At the end of study, we noted 66 % ovulation rate, 28% pregnancy rate and 2 % incidence of multiple pregnancy. **Conclusion:** Ovulation induction should be considered as first line of management for the infertile women with PCOS should be done with clomiphene citrate. Initial evaluation and proper patient selection improves pregnancy rates.

Key Words: ovulation induction, polycystic ovary syndrome, clomiphene citrate, pregnancy rate.

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INTRODUCTION

Ovulatory dysfunction is an important and common cause of failure of reproduction in cases of female infertility and it is mainly caused by hypothalamic-pituitary failure/dysfunction and ovarian failure. Anovulatory infertility is responsible for approximately 40% of cases of female infertility.[1] Normogonadotrophic anovulation, also classified as World Health Organization group II anovulation, is the most common category of anovulatory infertility. Within this group, polycystic ovary syndrome (PCOS) is by far the most prevalent cause, accounts for 85% of anovulatory females.[2] With increasing modernization, its prevalence is growing rapidly. Other

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than polycystic ovary syndrome (PCOS) causes of anovulation may be obesity, extreme weight loss, exercise or other stress, hyperprolactinemia, pituitary tumors, or thyroid disease. Anovulatory infertility requires evaluation to detect underlying systemic disease, followed by specific treatment.[3] It is a known fact that PCOS is associated with insulin resistance and metabolic disturbances. Hyperandrogenism, obesity, insulin resistance, metabolic syndrome, and other endocrine abnormalities are proven associations or results of PCOS.[4] From conception, women with PCOS and their infants are at increased risk of perinatal complications, including gestational diabetes, pre-eclampsia, preterm labour, and neonatal morbidity.[2,5] Clomiphene citrate is a non-steroidal triphenylethylene derivative that exhibits both estrogenic agonist and estrogenic antagonist properties. Its mechanism of action for ovulation induction is by competitive binding to estrogen receptors in the hypothalamus and pituitary reducing signalling of estrogen via its receptors. This interferes with the feedback mechanism of endogenous estrogen resulting in an increase in FSH and LH secretion to stimulate ovarian follicular production.[6] Anti-estrogenic effect of clomiphene leads to prolonged depletion of estrogen receptors, , resulting in a thin endometrial lining and poor cervical mucus.[7] Induction of ovulation in PCOS women is a challenge and the best ovulation induction drug is still debatable. In present study we assessed effectiveness of clomiphene citrate for ovulation induction and pregnancy rates in infertile women with polycystic ovary syndrome.

MATERIAL AND METHODS

Present study was a prospective, observational study conducted in department of obstetrics and gynaecology. Study duration was 2 years (January 2018 to Dec 2019). Institutional ethical committee approval was taken.

Inclusion criteria –

Women with primary/secondary infertility, with PCOS, willing to participate and follow up. Diagnosis of PCOS was made on Rotterdam criteria. According to the Rotterdam criteria, PCOS is diagnosed by at least two out of three features: presence of oligo- or anovulation, evidence of clinical or biochemical hyperandrogenism and ultrasound appearance of polycystic ovaries.[8]

Exclusion criteria

- Age ≥39 years
- Women previously taken treatment with CC
- Patients with hyperprolactinemia, thyroid disorder, male factor infertility, suspected tubal factor, endometriosis and unexplained infertility.
- women with uterine/ adnexal pathology e.g. fibroid,
- with impaired hepatic/renal function.

Procedure was informed in local language and consent was obtained from all patients enrolled in the study. The patients enrolled in this study were subjected to clinical examination, clinical evidence of acne, hirsutism, acanthosis nigricans, hyperthyroidism and hypothyroidism were looked BMI was calculated as BMI = weight in kg/height in m2 , in all patients enrolled in this study. Complete blood count, random blood sugar, renal function test and liver function test done in all patients. Initially dose of 50 mg of CC was given for 5 days, from postmenstrual day 2. Follicular monitoring was done by transvaginal sonography starting on day 8 of menstrual cycle till a follicle attained 18-25mm diameter. A single injection of HCG 10,000 IU was given IM if at least one follicle attained 17-18 mm. Timed intercourse was advised to the patient after 24-36 hrs of HCG injection. A final scan after 48 hrs was done for all patients to confirm rupture of follicle. If not ruptured, a repeat scan was done after 72 hrs to diagnose luteinized unruptured follicle. Ovulation was confirmed by sonographic finding and day 21 serum progesterone. Serum P4 on day 21 was done for all patients. Serum beta human chorionic gonadotropin (βHCG) was done after one week of missed periods to confirm the pregnancy. Initially ovulation induction done with starting dose of 50 mg/day for 5 days during the follicular phase. If ovulation does not occur, the dose is increased by 50 mg in the next cycle after a progesterone-induced withdrawal bleeding. Total maximum 6 cycles were given with maximum dose of 150 mg. Ongoing pregnancy diagnosed following visualization of cardiac activity by TVS. Clomiphene Resistance was defined as absent of ovulation i.e. absence of follicular development on TVS after treatment with CC (150mg for 5 days in 3 cycles). Primary outcome measures are ovulation rate, endometrial thickness, mono Vs. multifollicular rate, and days to ovulation, pregnancy rate. Statistical analysis was done using descriptive statistics.

RESULTS

Initially 70 patients were recruited in present study. 64 patients either conceived or taken treatment for complete 6 months were considered for present study. Most common age group was 21-25 years. Mean age of study patients was 26.1 ± 3.3 years. 55% patients had normal BMI while 34 % were overweight. 77% patients had primary infertility. 73% patients had 1-5 years duration of infertility. 30% patients had history of laparoscopic ovarian drilling. Hirsutism was noted in 58%.

Table 1: Clinical profile

Clinical Profile		No. of patients	Percentage (%)	Mean ± SD
Age	21-25 years	31	48%	26.1 ± 3.3 years
	26-30 years	26	41%	
	31-35 years	7	11%	
	>36 years	1	2%	
Body mass index (kg/m2)	Underweight (< 18.5)	2	3%	24.41 ± 3.19 kg/m2
	Normal (18.6-24.9)	35	55%	
	Overweight (25-29.9)	22	34%	
	Obese (30-39.9)	4	6%	
Type of Infertility	Primary Infertility	49	77%	
	Secondary Infertility	15	23%	
Duration of Infertility	1-5 years	47	73%	4.51 ± 4.19 years
	6-10 years	13	20%	
	>10 years	2	3%	
History of Laparoscopic ovarian drilling		19	30%	
Hirsutism		37	58%	

After serial USG examinations, at the end of study monofollicular development (55 %) was more common than multifollicular development (45 %). Mean endometrial thickness was 7.82± 2.29 mm. Average days for ovulation with clomiphene citrate were 14.6 ± 3.94. On day 21, average P4 values were 11.15 ± 6.81 ng/ml.

Table 2: Outcome of ovarian stimulation

Outcome	No of patients (%) / Mean ± SD
Monofollicular development	35 (55 %)
Multifollicular development	29 (45 %)
Endometrial thickness (mm)	7.82± 2.29
Days to ovulation	14.6 ± 3.94
P4 on Day 21(ng/ml)	11.15 ± 6.81

At the end of study, we noted 66 % ovulation rate, 28% pregnancy rate and 2 % incidence of multiple pregnancy.

Table 3: Treatment outcome

Outcome	No of patients (%)
Ovulation rate	42 (66 %)
Pregnancy rate	18 (28 %)
Multiple pregnancy	01 (2 %)

DISCUSSION

Anovulation and oligo-ovulation are estimated to be the cause 21% of female infertility.[9] Diagnosis of ovulatory dysfunction is established by menstrual history, timed serum progesterone determinations (during the putative luteal phase), monitoring urinary pregnanediol glucuronide excretion, or serial transvaginal ultrasound examinations. In women with WHO group II anovulation including anovulatory PCOS, expectant management is not recommended, because pharmacological ovulation induction significantly improves pregnancy rate compared with placebo no treatment.[10] Among all the drugs currently available, clomiphene citrate (CC) remains the most commonly prescribed ovulation-inducing medication and is probably the most appropriate initial choice in the majority of anovulatory infertile women. Mood swings are the most common side effect (64%–78%), whereas vasomotor flushes (hot flashes) occur in approximately 10% of CC-treated women. These side effects typically abate soon after treatment ends. In present study with 64 women we did not noticed such side effects. After serial USG examinations, we noted multifollicular development in 45 %. Similar results were noted by Hegde R (38.1% - multi-follicular development).[11] Although the numbers of follicles developed per cycle by using clomiphene citrate was higher; nevertheless, it increases the chances of ovarian hyperstimulation syndrome and multiple pregnancy.[13] In present study 1 patient had twin gestation, none of our patient developed ovarian hyperstimulation syndrome. Endometrial thickness is the maximal thickness of the endometrial lining in the plane through the central longitudinal axis of the uterine body. In women with WHO group II ovulatory disorders, ovulation induction with CC might result in lower EMT than other ovulation induction regimens. Whether the lower EMT caused the lower pregnancy and live birth rates remains to be elucidated.[14] In our study, the mean endometrial thickness was 7.82± 2.29 mm. Other Indian studies noted mean endometrial thickness with clomiphene citrate as 7.86 ± 1.25 mm[12] and 7.18±0.72 mm.[14] Higher ovulation rate as 84 % was

reported by Hegde R[12], which is much higher than present study (66%). Sahu M,[15] noted pregnancy rate after ovarian stimulation with clomiphene citrate as 12%, we noted better pregnancy rates as 28%. Clomiphene citrate is the main treatment for women with anovulatory infertility due to polycystic ovarian syndrome. But, about 15-20% of PCOS patients do not respond to clomiphene therapy. In present study 12% cases had clomiphene resistance. Cheng J *et al.* defined CC resistance as: "Anovulatory women who do not ovulate while receiving the 150 mg dose of Clomiphene citrate". CC resistance accounts for about 25%.[16] Reasons for CC resistance are unclear; it may be due to the anti-estrogenic effect of CC on endometrium, cervical mucus and associated high LH, resulting in luteal phase dysfunction.[17] Unexplained infertility usually refers to couples in whom all the standard investigations such as tests of ovulation, tubal patency and semen analysis are normal. Clomiphene citrate treatment combined with intercourse does not increase cycle fecundity in couples with unexplained infertility compared with expectant management.[18] Miscarriage rate is higher than general population and 20-25% PCOS women are resistant to clomiphene. Anti-estrogenic effect of clomiphene leads to prolonged depletion of estrogen receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus.[19] In a meta-analysis, letrozole was compared with clomiphene for ovulation induction in PCOS women. They noted no significant differences in pregnancy rate, abortion rate, and multiple pregnancy rate between the two groups.[20] NICE guidelines state that first-line treatment for WHO group 2 anovulation should be clomiphene citrate for up to 12 months.[21]

CONCLUSION

Ovulation induction should be considered as first line of management for the infertile women with PCOS should be done with clomiphene citrate. Initial evaluation and proper patient selection improves pregnancy rates.

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