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CLINICAL ANALYSIS OF CLOMIPHENE CITRATE INDUCED OVULATION IN INFERTILITY PATIENTS WITH POLYCYSTIC OVARIAN DISEASE

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Abstract

Background: Normo-gonadotrophic anovulation is the most prevalent anovulatory infertility type. Polycystic ovary disease (PCOS) is by far the most common cause in this category, accounting for 85 % of females who are anovulatory. Its prevalence is growing increasingly with increasing modernisation. Ovulation induction in PCOS females is a problem and the best drug for ovulation induction is still debatable.

Aims & objectives: In the current research, we evaluated the efficacy of clomiphene citrate in infertile women with polycystic ovary disease for ovulation induction and pregnancy rates.

Material and Methods: The present research was a prospective study conducted with PCOS, willing to participate and follow up in women with primary/secondary infertility. Rotterdam criteria were used to diagnose PCOS. Using descriptive statistics, statistical analysis was performed.

Results: Initially, 140 patients in the current study were recruited. For the current research, 128 patients either born or cared for a full 6 months were considered. 21-25 years of age was the most common age group. The mean age of the patients examined was 26.34 ± 3.6 years. 55 % were having average BMI patients, while 34% were overweight. Primary infertility was present in 77 percent of patients. 73 per cent of patients had infertility duration of 1-5 years. 30 percent have a history of laparoscopic ovarian drilling in patients. In 58 percent, hirsutism was noted. Following serial USG monitoring, mono-follicular development (55 %) was more prevalent than multi-follicular development at the end of the study (45 percent). The mean thickness of the endometrium was 7.78 ± 2.58 mm. The mean days for clomiphene citrate ovulation are 14.84 ± 3.46. Average P4 values on day 21 were 11.48 ± 6.44 ng/ml. At the end of the study, 66 % ovulation rate, 28 % pregnancy rate, and 2 % multiple pregnancy incidence were noted.

Conclusion: Ovulation induction with clomiphene citrate should be considered as the first line of treatment for infertile women with PCOS. Initial assessment and careful selection of patients increases pregnancy rates.

Keywords: ovulation induction, polycystic ovary disease, clomiphene citrate, pregnancy rate.

Introduction

In cases of female infertility, ovulatory dysfunction is a significant and widespread cause of failure of reproduction and is primarily triggered by hypothalamic-pituitary failure/dysfunction and ovarian failure. For approximately 40 percent of cases of female infertility, anovulatory infertility is responsible[1,2]. Normo-gonadotrophic anovulation, also known as group II anovulation by the World Health Organization, is the most common anovulatory infertility type. Polycystic ovary disease (PCOS) is by far the most common cause in this category, accounting for 85% of females who are anovulatory[3,4,5]. Its prevalence is growing increasingly with increasing modernisation. Other than Polycystic Ovary Disease (PCOS), obesity, excessive weight loss, exercise or other stress, hyper-prolactinemia, pituitary tumors, or thyroid disease can be causes of anovulation. Anovulatory infertility, accompanied by specific care, requires assessment to diagnose underlying systemic disease. It is a known fact that PCOS is associated with insulin resistance and metabolic disorders[6,7]. Established associations or effects of PCOS are hyper-androgenism, obesity, insulin resistance, metabolic disease and other endocrine abnormalities. Women with PCOS and their children are at elevated risk of peri-natal complications from pregnancy, including gestational diabetes, pre-eclampsia, preterm labor, and neonatal morbidity. Clomiphene citrate is a non-steroidal form of triphenyl-ethylene[8,9]. Its ovulation induction mechanism of action is via competitive binding to hypothalamus oestrogen receptors and pituitary reduction of oestrogen signalling through its receptors. This interferes with the endogenous oestrogen feedback system, resulting in an increase in FSH and LH secretion to promote the development of ovarian follicles[10,11]. Clomiphene's anti-estrogenic effect contributes to sustained degradation of oestrogen receptors, resulting in a thin endometrial lining and weak cervical mucus[12].

Aims & objectives: In the current research, we evaluated the efficacy of clomiphene citrate in infertile women with polycystic ovary disease for ovulation induction and pregnancy rates.

Material and methods

The present research was a prospective study carried out in the obstetrics and gynaecology department. The length of the study was 2 years. Approval was received from the institutional ethics committee.

Criteria for inclusion: Women with primary/secondary infertility, with PCOS, able to engage and follow up. Rotterdam criteria were used to diagnose PCOS. PCOS is diagnosed with at least two out of three characteristics according to the Rotterdam criteria: the occurrence of oligo- or anovulation, signs of clinical or biochemical hyper-androgenism, and the existence of ultrasound polycystic ovaries.

Criteria for exclusion: Age > 39 years, women who have previously undergone clomiphene citrate (CC) therapy, patients with hyper-prolactinemia, thyroid disorder, male infertility factor, presumed tubal factor, endometriosis and unexplained infertility. Women with uterine/ adnexal pathology with compromised hepatic/ renal function, e.g. fibroids.

In the local language, the treatment was told and consent was obtained from all patients enrolled in the study. Clinical review, clinical proof of acne, hirsutism, acanthosis nigricans, hyperthyroidism and hypothyroidism were performed in patients enrolled in this research. In all patients enrolled in this study, BMI was measured as BMI = kg/height in m^2. All patients undergo full blood counts, random blood sugar, renal function tests, and liver function tests. Initially, a 50 mg CC dose was administered for 5 days, beginning on postmenstrual day. Follicular monitoring was performed beginning on day 8 of the menstrual cycle by trans-vaginal sonography until a follicle reached a diameter of 18-25 mm. A single dose injection IM of HCG 10,000 IU was given if at least one follicle reached 17-18 mm. After 24-36 hours of HCG injection, timed intercourse was recommended for the patient. A final scan after 48 hours was performed to confirm follicle rupture in all patients. A repeat scan was performed after 72 hours to diagnose the luteinized unruptured follicle, if not ruptured. Ovulation was confirmed by sonographic findings and progesterone serum on day 21. Serum P4 was performed for all patients on day 21. After one week of missing periods, serum beta human chorionic gonadotropin (βHCG) was carried out to confirm pregnancy. Initially, ovulation induction was performed at the starting dose of 50 mg/day during the follicular phase for 5 days. If ovulation does not occur, in the next cycle after progesterone-induced withdrawal bleeding, the dose is raised by 50 mg. A maximum number of 6 cycles were administered with a maximum dose of 150 mg. Diagnosis of continuous pregnancy after visualization of cardiac activity by TVS. Resistance to clomiphene was characterized as absence of ovulation, i.e. absence of follicular growth on TVS following CC treatment (150mg for 5 days in 3 cycles). Primary outcome measurements are ovulation rate & endometrial thickness. Using descriptive statistics, statistical analysis was performed.

Results

Initially, 140 patients in the current study were recruited. For the current research, 128 patients either born or cared for a full 6 months were considered. 21-25 years of age was the most common age group. The mean age of the patients examined was 26.34 ± 3.6 years. 55 % were average BMI patients, while 34 % were overweight. Primary infertility was present in 77 percent of patients. 73 per cent of patients had infertility duration of 1-5 years. 30 percent have a history of laparoscopic ovarian drilling in patients. In 58 percent, hirsutism was noted.

Table 1: Clinical profile

Clinical Profile		No. of patients	Percentage (%)
Age	21-25 years	62	48%
	26-30 years	52	41%
	31-35 years	12	11%
	>36 years	2	2%
Body mass index (kg/m2)	Underweight (< 18.5)	4	3%
	Normal (18.6-24.9)	70	55%
	Overweight (25-29.9)	46	34%
	Obese (30-39.9)	8	6%
Type of Infertility	Primary Infertility	98	77%
	Secondary Infertility	30	23%
Duration of Infertility	1-5 years	94	73%
	6-10 years	28	20%
	>10 years	6	3%
History of	Laparoscopic ovarian drilling	38	30%
	Hirsutism	74	58%

Following serial USG monitoring, mono-follicular development (55 %) was more prevalent than multi-follicular development at the end of the study (45 percent). The mean thickness of the endometrium was 7.78 ± 2.58 mm. The mean days for clomiphene citrate ovulation are 14.84 ± 3.46. Average P4 values on day 21 were 11.48 ± 6.44 ng/ml.

Table 2: Outcome of ovarian stimulation

Outcome No of patients	(%) / Mean ± SD
Monofollicular development	70 (55 %)
Multifollicular development	58 (45 %)
Endometrial thickness (mm)	7.78 ± 2.58
Days to ovulation	14.84 ± 3.46
P4 on Day 21(ng/ml)	11.48 ± 6.44

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

Table 3: Treatment outcome

Outcome	No of patients (%)
Ovulation rate	84 (66 %)
Pregnancy rate	36 (28 %)
Multiple pregnancy	02 (2 %)

Discussion

The cause of 21 percent of female infertility is estimated to be anovulation and oligo-ovulation. The diagnosis of ovulatory dysfunction is determined by menstrual history, timed determinations of serum progesterone (during the putative luteal phase), urinary pregnanediol glucuronide excretion testing, or serial trans-vaginal ultrasound exams[13,14]. Expectant management is not recommended for women with WHO Group II anovulation, like anovulatory PCOS, since the activation of pharmacological ovulation substantially increases the risk of pregnancy compared to placebo without medication. Clomiphene citrate (CC) remains the most widely prescribed ovulation-inducing medication of all currently available drugs and is potentially the most effective initial option in most infertile anovulatory women. The most common side effect (64 percent-78 percent) is mood swings, while in around 10 percent of CC-treated women, vasomotor flushes (hot flashes) occur. Usually, these side effects decline shortly after treatment finishes. We didn't find any side effects in the current study of 128 women[15]. We noted multi-follicular growth in 45 percent after serial USG examinations. Hegde R registered similar results (38 percent - multi-follicular development). While the number of follicles produced by the use of clomiphene citrate per cycle was higher; however, the risks of ovarian hyper-stimulation disease and multiple pregnancy are increased. In the current research, 2 patients had twin gestation, none of our patients experienced ovarian hyper-stimulation disease. Endometrial thickness through the central longitudinal axis of the uterine body is the maximum thickness of the endometrial lining in the plane[16,17]. Ovulation induction with CC could result in lower EMT than other ovulation induction regimens in women with WHO group II ovulatory disorders. It remains to be clarified whether the lower EMT caused the lower pregnancy and live birth rates. The mean endometrial thickness in our sample was 7.78 ± 2.58 mm. Other Indian studies recorded a mean endometrial thickness of 7.86 ± 1.25 mm and 7.18 ± 0.72 mm with clomiphene citrate. Hegde R, which is far higher than the current research, reported a higher ovulation rate of 84%. (66 percent). After ovarian stimulation with clomiphene citrate Sahu M noted pregnancy rate as 12 percent, , we noted better pregnancy rates as 28 percent . The principal treatment for women with anovulatory infertility due to polycystic ovarian disease is clomiphene citrate. But about 15-20 percent of patients with PCOS do not respond to therapy with clomiphene. 12 percent of cases in the current study had resistance to clomiphene. Anovulatory women who do not ovulate while receiving a 150 mg dose of Clomiphene citrate have been defined by Cheng J et al. as CC resistance." CC resistance accounts for about 25 percent[18,19]. CC resistance causes 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. Unexplained infertility typically applies to couples in which all standard investigations are common, such as ovulation tests, tubal patency and semen analysis. The rate of miscarriage is higher than in the general population and clomiphene is immune to 20-25 percent of PCOS women. Clomiphene's anti-estrogenic activity contributes to sustained degradation of oestrogen receptors, adversely affecting the growth and production of the endometrium, as well as the quantity and consistency of cervical mucus. In a meta-analysis, letrozole was compared in PCOS women with clomiphene for ovulation induction[20,21]. They noted no major variations between the two groups in pregnancy rate, abortion rate, and multiple pregnancy rate. NICE guidelines state that clomiphene citrate should be first-line treatment for WHO group 2 anovulation for up to 12 months.

Conclusion

Ovulation induction with clomiphene citrate should be considered as the first line of treatment for infertile women with PCOS. Initial assessment and careful selection of patients shows increased pregnancy rates. When treatment with CC alone fails to induce ovulation, combination therapies involving CC and other agents may be efficient. Alternative CC-resistant women's therapies include treatment with aromatase inhibitors or exogenous gonadotropins, and ovarian drilling in selected patients. To ensure its efficacy in ovulation induction, CC treatment should be controlled. CC treatment side effects are usually mild and well tolerated. An increased frequency of multifetal gestation (<10 percent) is the primary risk of CC care.

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