

Clomiphene Citrate for Ovulation Induction in Patients with Polycystic Ovarian Syndrome

M A CHOHAN F BUTT H MANSOOR T FALAK

Department of Obstetrics & Gynaecology, King Edward Medical University, Lady Willingdon Hospital, Lahore
Correspondence to Dr. Arshad Chohan, Associate Professor

Objective: To provide fertility assistance and to determine the response of clomiphene citrate in polycystic ovarian syndrome. **Design:** Observational study. Place and duration of study: Department of Obstetrics and Gynecology Lady Willingdon Hospital Lahore. Eighty-four patients of polycystic ovarian syndrome who required fertility assistance were subjected to clomiphene citrate therapy for duration of 12 months from February 2005 to January 2006.

Intervention: Clomiphene citrate (50-150mg) was administered from second to sixth day of menstrual cycle and TVS performed on 12th and 16th day of cycle for follicular growth, ovulation, endometrial thickness and echogenic pattern.

Main outcome measures: Ovulation, conception rate, miscarriage rate and ovarian hyperstimulation rate were assessed. In addition the thickness and echogenic pattern of the endometrium was observed in conceived group. **Results:** Forty-six patients (54.76%) ovulated in six cycles while twenty-seven (32.14%) remained anovulatory. Sixteen women (34.79%) conceived during the study period. Out of which ten women (62.5%) miscarried. Endometrial thickness did not differ ($P > .50$) between the conceived and non-conceived group but echogenic grade A pattern (75%) was observed during the conceived cycles ($P < .001$). **Conclusion:** Clomiphene citrate (CC) is a successful drug for ovulation induction in patients with polycystic ovarian syndrome. But the discrepancy in ovulation and pregnancy rate support that clomiphene citrate therapy has antiestrogenic effect at the endometrium, which interferes with implantation of pregnancy. The high miscarriage rate in these patients demand some other forms of therapies. These include weight reduction, use of insulin sensitizing drugs, gonadotrophin therapy and ovarian drilling to reduce high LH levels, thus correcting disturbed hormonal milieu, ovulation resumption and pregnancy outcome.

Key words: Polycystic ovarian syndrome, clomiphene citrate, gonadotrophins, endometrial thickness.

The desire to procreate is an innate one. Every married couple wants to reproduce with very few exceptions. A fairly good proportion of the world population is suffering from infertility, which may profoundly upset an individual or couple psychologically. In Pakistan, infertility is even more distressing due to cultural bound customs and may result in rejection, divorce and second marriage.

In about 35% of the infertile couples, anovulation is the underlying cause that is potentially treatable. Polycystic ovarian syndrome (PCOS), a disease of unknown etiology is the most commonly diagnosed female endocrinopathy affecting, approximately 6% of the women of reproductive age group and contributes to infertility by causing anovulation¹. It is heterogeneous disorder with wide spectrum of clinico-pathological findings. At one end of the spectrum there is single finding of polycystic ovarian morphology as detected by pelvic ultrasound. At the other end of the spectrum symptoms such as obesity, hyperandrogenism, menstrual cycle disturbance and infertility may occur either singly or in combination.

The literature shows that PCOS is an endocrinopathy resulting from insulin resistance and the compensatory hyperinsulinaemia. This results in adverse effect on multiple organ systems and may result in alteration in serum lipids, anovulation, abnormal uterine bleeding and infertility. In addition the polycystic ovarian syndrome may place the patient at long-term risk for the development of type II diabetes, hypertension, endometrial cancer, and cardiovascular disease.

Despite extensive research and published literature, PCOS is an enigmatic disease worldwide. Its etiology and pathology is still poorly understood and consequently no single agent has been discovered to be effective or curative.

Many treatment modalities have been proposed and implemented in an effort to circumvent the intrinsic block to ovulation and thus restoring fertility. Clomiphene citrate is the most commonly used first line treatment modality for induction of follicular growth and ovulation. It is successful in inducing ovulation in over 80% of women, pregnancy only occurs in 30-40% of cases^{2,3}. Thus the discrepancy between the rate of ovulation and number of successful pregnancies is due to the anti-estrogenic effect of this drug on the endometrium. Controversy exists regarding the prognostic significance of endometrial pattern and thickness for the establishment of pregnancy in infertile women. Some investigators have suggested that both endometrial pattern and thickness influence the treatment cycle, but others argue that one characteristics play a more important role than the other⁴.

Patients with polycystic ovarian syndrome are poor responder to clomiphene citrate therapy and may often require assisted reproductive techniques because of intractable anovulation, failure to conceive inspite of stimulated ovulatory cycle. In this group of patients, the ideal method to achieve appropriate response to superovulation remains a dilemma. The risk of ovarian hyperstimulation syndrome (OHSS) can lead to high cycle cancellation rates, poor oocyte quality may result in low

fertilization rates and hence low pregnancy rates and high miscarriage rate (30%) is always disappointing.

Polycystic ovarian syndrome is a complex problem and the difficulty in treating the patients with fertility deprivation has led us to study the disease in particular. By the results of this study, we are not only being better able to define the influence of treatment on ovulation, conception and miscarriage rate but also on endometrial maturation in clomiphene citrate treatment cycles.

Materials and methods:

This study was carried out in the department of Obstetrics and Gynaecology Lady Willingdon Hospital Lahore in one-year duration from February 2005-January 2006. A total of eighty-four patients of polycystic ovarian syndrome who required fertility assistance were recruited in the study during the first 6 months. They were all subjected to clomiphene citrate therapy by using temporal sampling. It was an observational study. The Inclusion criteria were all patients between age of 21-35 years, who have clinical, biochemical and ultrasonographic (USG) diagnosis of polycystic ovarian syndrome and polycystic ovarian syndrome was the only recognizable cause of anovulation. Patient having polycystic ovarian disease alone on USG without the clinical stigmata of PCOS with raised serum prolactin level and serum TSH level were excluded.

The patients were booked for study after having an informed consent. The diagnosis of polycystic ovarian syndrome was confirmed by-history of Oligo/amenorrhea, infertility, hirsutism and obesity. A thorough general physical and pelvic examination was performed and the diagnosis of PCOS was confirmed by polycystic appearance of ovaries and raised level of LH and LH/FSH ratio on investigations.

The patients were counseled regarding treatment, dosage, effects and follow up. Clomiphene citrate was given in dosage of 50mg-150mg/day from 2nd to 6th day of menstrual cycle in a standardized incremental fashion, titrated to the minimum effective ovulation inducing dosage. Treatment was continued for up to six consecutive cycles. Transvaginal ultrasonography was done on 12th day of menstrual cycle for the size of dominant follicle (18-25mm) in each ovary and their number. The measurement of follicle was taken in mean diameter (two dimensions). In addition endometrium assessment was also done. The endometrial thickness was measured in sagittal plane. The distance from hyperechogenic interface between the endometrium and myometrium to the opposite interface including the midline echo (endometrial interface), which represented twice of the endometrial thickness was measured. The highest value of thickness in the plane was recorded. Endometrial grading was done according to following criteria; TYPE A. multilayer trilaminar pattern, TYPE B. isoechoic or intermediate pattern and TYPE C hyper

echoic pattern. Transvaginal USG was repeated on 16th day of menstrual cycle to confirm ovulation by the change in size and character of dominant follicle, presence of fluid in pouch of Douglas and endometrial thickness. Once ovulation was achieved at any given dosage, the treatment regimen then remained fixed for all subsequent cycles.

The data was collected using research proforma, and was analysed on computer using SPSS 10.0, applying "t" test for numerical data and Chi-square for nominal data. Data was analyzed regarding response to therapy, ovulation, no response, conception, miscarriage and ovarian hyper stimulation syndrome

Results:

During the period of one year i.e. from February 2005 to January 2006, a total of eighty-four patients were subjected to clomiphene citrate therapy. These patients were followed up for six months.

The average age of the study group was 28.5 SD±7.5 years. Majority of them (57.15%) had body mass index of >25kg/m². About sixty-six patients (78.57%) suffered from primary infertility and about eighteen patients (21.43%) from secondary infertility. Among those with secondary infertility twelve had first trimester abortion and six had delivered term babies.

The duration of infertility ranges between 2-8 years with mean duration of 5±2.1 SD. Patients took clomiphene citrate in a dosage of 50-150mg /day from 2nd to 6th day of menstrual cycle. Initially fifty-seven patients responded to therapy while twenty-seven (32.14%) remained anovulatory. Among those fifty-seven in whom ovulation occurred, it was maintained in only forty-six patients (54.76%) in subsequent cycles while eleven patients became unresponsive to therapy in later cycles. Sixteen women (34.79%) conceived out of forty-six in whom ovulation was maintained, while in thirty women (65.21%), there was no conception (Table 1).

Unfortunately, ten women (62.5%) miscarried within first two trimesters (Table- 2). Six of them delivered at term, only one patient had ovarian hyperstimulation syndrome that was managed conservatively.

During this study various characteristics of the women who conceived were compared with those who did not. The conception rate was 75% (P<001) statistically significant, among women of PCOS with secondary infertility as compared with primary infertility (25%). BMI shows an inverse relationship with conception rate, thus more patients (68.75%) conceived with BMI of <25kg/m² than (31.5%) with BMI of >25kg/m² (P<02). This was statistically significant (Table-3).

In the conceived group seven patients (43.75%) had endometrial thickness of 5-10mm and nine (56.25%) had >10mm thickness on the 12th day of cycle. In comparison, in the non-conceived group sixteen patients (53.33%) had 5-10mm thickness while remaining fourteen (46.67%) had

>10mm endometrial thickness. $P >.50$, that was not statistically significant.

The echogenic pattern of the conceived versus non-conceived group was also studied as uterine receptivity is an important event for implantation of pregnancy. About 75% of the patients ($P<001$), who conceived showed echogenic grade A pattern of endometrium, 6.25% had grade B pattern ($P<02$) and 18.75% had grade C endometrial pattern ($P>.50$) as compared with non-conceived group which show 16.6% grade A pattern, 40% had grade B, and 43% had grade C pattern.(Table 4)

Table 1: Conception in the Study Group (n=46)

Conception	=n	%age
Conceived	16	34.79
Non conceived	30	65.21

Table 2: Out come of Pregnancy (n=16)

Pregnancy outcome	=n	%age
Abortion	10	62.50
Termed delivery	06	37.05

Miscarriage Rate 62.5%

Table 3: Comparison of Body mass index in conceived and non-conceived Group (n=16)

Body mass index	Conceived group	Non conceived group
<25	11(68.75%)	10(33.33%)
>25	5(31.25%)	20(66.67%)

$P < .02$ Statistically Significant

Table 4: Comparison of endometrial pattern in conceived and Non -conceived Group (n=16)

Endometrial pattern	Conceived group	Non conceived group
A	12(75%)	5(16.66%)
B	1(6.25%)	12(40%)
C	3(18.75%)	13(43%)

$P < .001$ Statistically Significant

Discussion:

The prevalence of polycystic ovarian syndrome in women with fertility deprivation has been well documented. Although there are multiple causes of infertility, 15-25% of patients attending infertility clinics are suffering from anovulation. In one study of 708 infertile couples, defective ovulation was found to be a sole factor in 21% of the couples⁵. PCOD is one of the commonest endocrinopathy in the women of reproductive age, which leads to anovulation.

Mean age of our patients was (28.5 SD±7.5) years, while in a large study, of 1741 women conducted by Balen⁶ the mean age was 31.5 years. The results can be explained by smaller sample size involving infertility as selected symptom while Balen included all cases of PCO either fertile or infertile.

Obesity was a cardinal sign in original description of PCOS by Stein Leventhal but its presence is extremely

variable. Among, the PCOS group as the BMI increased, the conception rate decreased. In our study 57.15% of patients had BMI of >25kg/m² and 42.85% had BMI of <25kg/m². The conception rate was higher 68.75% among those who had BMI of <25kg/m², ($P<.02$) statistically significant. The results are comparable to the study conducted by Rana S⁷ in which the conception rate was 57% among women with BMI of <25kg/m². In our study, as the BMI increased to >25kg/m², conception rate fell down to 31.25% showing obesity to be a significant factor in hindering conception as these women are more likely to be anovulatory, hirsute and had lower levels of Sex Hormone binding globulin, and higher free testosterone. Weight loss is associated with normalization of hormonal disturbance and resumption of regular ovulation. It is recommended that BMI of <25kg/m², should be the aim for obese and hirsute women.

In our study about 78.57% of patients had primary infertility while 21.43% had secondary infertility. This implies that in most of the cases disease manifests earlier in reproductive life and after marriage, the patients seek advice for conception since they experience difficulty in conceiving without help. Secondary fertility deprivation may evolve at a later stage i.e. after having one or more conceptions or it may simply follow through of a problem which the patient might have experienced even before her previous pregnancies (with or without treatment). Conception rate was higher about 75% in women with secondary infertility as compared with primary infertility. PCOS patients respond well to clomiphene citrate therapy as it induces ovulation in 70-85% of cases⁸. In our study maintained ovulation in six cycles was 57.76%, while 32.14% remained anovulatory. The results are comparable to another study in which ovulation rate was 70% in study group⁹.

The response of therapy was determined in terms of ovulation but PCOS patients are notorious, they might become unresponsive to therapy after having been ovulated and may require higher dosage of clomiphene citrate, gonadotrophin therapy or ovarian drilling. In our study about eleven patients (13%) became refractory to therapy after having ovulated twice or thrice. This is compared with study in which 15% patient failed to ovulate after having responded to the same treatment regimen in previous cycles.¹⁰

In our study conception rate was 34.79%, the results are comparable to the study of Speroff l¹¹ in which the pregnancy rate approached only to 40% although ovulation rate was 70%, supporting the discrepancy between the ovulation and conception in clomiphene citrate therapy.

A miscarriage rate of about 62.5% was observed, which was very disappointing. The reasons behind such a high miscarriage rate remain unknown but there is an association between raised LH levels and miscarriage rate. It is possible that elevated LH may have an adverse effect on the process of oocytes maturation, may induce

premature luteinization and adversely affect the endometrial maturation. The results are comparable to a study which confirmed that women who had a normal follicular phase LH, the miscarriage was 12% while those with elevated LH had a miscarriage rate of 65%. Such a miscarriage rate in my study indicates that selected group had higher LH levels¹².

The discrepancy between the rate of ovulation (57.76%) and pregnancy rate (34.79%) might result from anti-estrogenic affect of CC on the endometrium. As implantation is an important event for pregnancy and depends on the uterine receptivity, thus the character of endometrium including both the thickness as well as echogenic grading was also taken into consideration. The thickness of endometrium of both conceived and non-conceived groups showed no statistically significant difference ($P > .50$). The results are comparable to large study conducted by Dickey and coworkers, in which they found no difference in endometrial thickness in both the conceived group and non-conceived group¹³.

In the conceived group about 75% of the patients shows grade A endometrial pattern, favorable for implantation. The results were statistically significant ($P < .001$). The results were comparable to the study conducted by Yasuiko Nakamarru in which 72% of the patients who conceived showed echogenic grade A pattern¹⁴.

All the above findings point to the fact that women with full blown picture of PCOS, the conception rate was low even with clomiphene citrate therapy and the high miscarriage rate points that reduction in the level of LH level either by use of gonadotrophin, weight reduction or use of insulin sensitizing agents might be helpful in improving the hormonal status, ovulation resumption, insulin resistance and pregnancy outcome.

Conclusion:

The occurrence of a fertility problem for a couple, though common, is generally unanticipated. It is often deeply painful and therefore deserves help. So it become duty of the clinicians to counsel them and offer them the best option they have.

Clomiphene citrate is successful drug in ovulation induction. But the discrepancies in ovulation and pregnancy support that CC have anti-estrogenic affects at the endometrium, which interfere with implantation of pregnancy. The high miscarriage rate in these cases demands some other forms of therapies. Therefore in these patients weight reduction, use of insulin sensitizing agents, gonadotrophin therapy and ovarian drilling should be

considered to reduce LH surge, hyperinsulinaemia, thus correcting the disturbed hormonal milieu, ovulation resumption and pregnancy outcome.

Keeping in mind the circumstances in our country, we strongly feel that CC should be considered as first step in the provision of fertility assistance in these patients, as it is cost affective, needs less intensive monitoring, provided it is taken in proper dosage and the response of therapy is monitored by serial ultrasonography.

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