



## FREQUENCY AND OUTCOME OF TREATMENT IN PCOS RELATED INFERTILITY

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ARTICLE INFO	ABSTRACT
<p><b>Keywords:</b> Polycystic Ovarian Syndrome (PCOS), Female infertility, Ovulation induction, Clomiphene citrate, Metformin, Gonadotrophins</p> <p><b>Corresponding Author: Dr Ayesha Fatima,</b> PGR Gynea &amp; Obs, DHQ Teaching Hospital Mirpur, Ajk, Email: <a href="mailto:fatoashi39@gmail.com">fatoashi39@gmail.com</a></p>	<p><b>Background:</b> The inability of a couple to conceive after a year of unprotected sexual activity is known as infertility. In Pakistan, infertility is 21.9% of the population. Polycystic ovarian syndrome (PCO) is the most prevalent cause of infertility that can be treated medically. The purpose of this study was to determine the prevalence of PCO-related infertility and the results of treatment for infertile couples who visited Gynecology department Divisional Headquarters Teaching Hospital Mirpur ajk.</p> <p><b>Methods:</b> Gynecology department Divisional Headquarters Teaching Hospital Mirpur ajk hosted this prospective observational study for three months, from aug to oct 2023. This study covered 160 infertile couples in total.</p> <p><b>Result:</b> 37.5% of female-related infertility cases had PCOs. Other reasons of infertility in women included endometriosis (9.3%), hyperprolactenemia (1.8%), hypothyroidism (1.25%), and pelvic inflammatory illness (43.7%). Various forms of treatment were administered to PCOS patients. 58.3% of the 160 PCO patients who received clomiphene citrate for ovulation induction became pregnant. A combination of metformin and clomiphene citrate was administered to TWENTY women. 13 of them (65%) became pregnant. Two (40%) of the five patients who received gonadotrophins became pregnant. TWO (20%) of the 10 patients who had laparoscopic drilling became pregnant.</p> <p><b>Conclusion:</b> Contrary to the literature research, the second most common cause of infertility in women was found to be polycystic ovarian syndrome. However, as evidenced by the global literature, it had excellent results following medical and/or surgical intervention.</p>

## INTRODUCTION

Infertility is a global issue that affects the affected person on a deep social and emotional level. More than 186 million ever-married women in developing nations (apart from China) were infertile due to primary or secondary infertility, infertility, and childlessness in developing nations, according to the WHO, DHS Comparative Report from 2004. One With a population growth rate of about 2% and one of the most populated nations in the world today, Pakistan also has a high prevalence of infertility (21.9%); the main rate is 3.5% and the secondary rate is 18.4%.<sup>2</sup>

Infertility in women has many possible causes. The most common cause of treatable infertility is polycystic ovarian syndrome, common in young women and cause of an ovulatory infertility in 70% cases.<sup>3</sup> The World Health Organization classification offers a useful frame for diagnosis and treatment. Polycystic ovary syndrome is the most common cause of oligo ovulation and anovulation.<sup>4</sup> Polycystic ovarian syndrome (PCOS) is a common endocrine disorder which causes anovulatory infertility.<sup>5</sup> In PCOS Increased ovarian androgen production leads to premature adrenarche, menstrual irregularity, acne, hirsutism, and infertility by means of elevated luteinizing hormone to follicle stimulating hormone production and hyperinsulinemia. <sup>6</sup>

The disorder known as polycystic ovarian syndrome is diverse. The following are the suggested diagnostic criteria for polycystic ovaries: clinical and/or biochemical indicators of hyperandrogenism, as well as irregular menstruation brought on by oligo or ovulation.

exclusion of other conditions, such as androgen-secreting tumors and non-classical congenital renal hyperplasia. <sup>7</sup> .Two of the three conditions listed below must exist in order for Rotterdam criteria to diagnose PCO. oligo-or an ovulation, biochemical and/or clinical indicators of hyperandrogenism, and ultrasound evidence of polycystic ovarian proliferation. <sup>8</sup>

The Androgen Excess Society (AES) states that all of the following should be present in order to diagnose PCO: 1. Clinical and/or biochemical evidence of hyperandrogenism. 2. Ovarian dysfunction: polycystic ovaries and/or oligo-an ovulation on ultrasonography 3. Elimination of ovulatory abnormalities or other excess androgens. <sup>9</sup> It is important to look at couples who have been trying to conceive for one to two years. It is necessary to conduct a thorough history, examination, and inquiry of both spouses. A history of a regular menstrual cycle in females suggests ovulation. Mid-luteal serum progesterone levels (>30 nmol/L Androstenedione levels), FSH and LH levels, and GnRH stimulation are used to confirm ovulation. Eliminate any further conditions that may cause hyperandrogenism and irregular menstruation, such as ovarian or adrenal tumors, thyroid issues, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, and Cushing syndrome. <sup>10</sup> Thyroid function test (e.g., TSH, free thyroxin), serum prolactin level, total and free testosterone levels, free androgen index, serum HCG level, cosyntropin stimulation test, serum 17-hydroxyprogesterone (17-OHPG) level, urinary free cortisol (UFC), and creatinine are among the baseline screening laboratory tests for women suspected of having PCOS. serum insulin-like growth factor (IGF)-1, low-dose dexamethasone suppression test, and levels. level A glucose level and an insulin level are two more tests used to assess PCOS. <sup>11</sup> In terms of management, women with PCOS are thought to benefit most from lifestyle changes. These modifications consist of the following: Twelve Weight loss, exercise, and diet. Within six months, 55–100% of obese women with PCOs may regain their ability to conceive after losing 5–10% of their body weight. <sup>13</sup>

The preferred treatment for women with polycystic ovarian syndrome who have irregular ovulation is clomiphene citrate, an oral active synthetic substance with both estrogenic and anti-estrogenic effects. It is anticipated that 80% of women using clomiphene will ovulate, and 35–40% will become pregnant. 14. About 20–25% of women are regarded as resistant since they do not respond to clomiphene citrate. It has been hypothesized that reducing insulin levels would improve the clinical and metabolic profile of women with PCOS due to the strong correlation between insulin resistance and ovulation. Compared to placebo, metformin is more successful in causing ovulation in women with PCOs. 15. Another approach for treating women with PCO-associated ovulation is laparoscopic ovarian drilling (LOD), which involves diathermy or laser. Four punctures are made into each ovary, each 4 mm deep, using a unipolar coagulation current. 4. According to a review by Chechrance, the continuous cumulative pregnancy rate after LOD was comparable to that attained with gonadotrophin cycles of three to six. 4. Comparing laparoscopy ovarian drilling to competing chemotherapy treatments reveals a clear advantage. It may be the preferred course of treatment for women with CC-resistant PCOS if it lowers the overall cost of care and multiple gestations. 16

**Gonadotrophins:** When a woman does not respond to clomiphene or does not conceive after 6–12 ovulatory cycles, treatment with gonadotrophins is considered. Gonadotrophin treatment increases the cumulative pregnancy rate in women with PCOs by 40–50%. 17. GnRH analogs: To accomplish pituitary downregulation and aid in cycle control, GnRH analogs have been utilized in combination with gonadotrophins. A systematic evaluation of three randomized controlled trials (RCTs) found no additional pregnancy-rate benefits linked to the combination of gonadotrophins and GnRH analogs. 18

**METHODS** Gynecology department Divisional Headquarters Teaching Hospital Mirpur ajk.Pakistan, hosted this prospective observational study for three months, from aug to oct 2023. Within this study, 150 couples were involved. Every infertile woman was evaluated using a thorough history, a full physical examination, serum day-21 progesterone levels, pelvic ultrasound, a tubal patency test using either hysterosalpingography or laparoscopy, and various hormonal analyses. Among other things, there included serum prolactin levels and thyroid profiles. Tests for GnRH stimulation, serum FSH, serum progesterone, serum testosterone, glucose, and insulin levels, among others. BMI, height, weight, and age were considered female variables. Every investigation's findings were assessed. We diagnosed PCOS using the Rotterdam criteria. Various treatments were administered based on the findings of the inquiry, which include the following.

**1. Clomiphene citrate tablet for ovulation induction:** 5 mg of clomiphene citrate daily for 5 days, starting on the second day of the menstrual cycle. If no result is obtained after 5 days, the dosage is increased to 100 mg in the second cycle, starting on the second day of the menstrual cycle. The dosage of clomiphene citrate was raised to 150 mg per day starting on the second day of the menstrual cycle and continued for five days in the third menstrual cycle when no results were obtained.

**2. Clomiphene citrate with metformine.** Women who were obese were treated with metformin and clomiphene citrate at a dose of 250 mg twice daily for six months, along with the same dosage of clomiphene citrate.

**3. Gonadotrophins for ovulation induction:** In the event that clomiphene citrate induction was

unsuccessful, injectable gonadotrophin was administered to induce ovulation using the following protocol: 75 IU was administered intramuscularly. For ten days, the injection was administered every day starting on the second day of the menstrual cycle. Twice a week, ultrasound surveillance was performed to rule out ovarian hyperstimulation. The injection was repeated until one or two mature follicles measuring around 18 mm were visible on ultrasonography. About 36 hours later, an injection of 5000 IU of HCG was administered to start ovulation. After three to six months of trying this regimen with no results, the couple was referred for in vitro fertilization.

**4. Clomiphene citrate ovarian drilling:** The pair was offered laparoscopic ovarian drilling or human menopausal gonadotrophins as a second line of treatment if a course of clomiphene citrate did not result in conception.

**RESULTS**

160 (5.3%) of the 3000 women that visited the gynecological OPD, throughout the study period, experience infertility . In 150 (93.75%), female factors were discernible. Among them, 70 (43.7%) women had pelvic inflammatory illness, which appears to be the main cause in this study and relates only to infection of the female upper genital tract (the female tissues above the cervix). PCO was the second reason for female infertility, affecting 60 women (37.5%). Additional reasons why women are infertile were found to be 11% endometriosis and 8% hyperprolactinemia, or an excess of Blood prolactin is typically brought on by pituitary adenoma, although it can also occasionally be brought on by endocrine adverse effects from specific antipsychotic drugs. It is typically linked to 1.35% hypothyroidism in women as well as galactorrhea and secondary amenorrhea. Thyroid hormone, which is typically produced by the thyroid gland, which is situated at the front of the neck, is deficient.

The study excluded all patients except those with PCO, and the PCO patient's treatment outcomes were monitored going forward. (Table I)

TABLE 1				
Pelvic	Inflammatory	disease	70	43.7%
Polycystic	Ovarian	Syndrome	60	37.5%
Endometriosis	15	9.3%		
Hyperprolactinemia	3	1.8%		
Hypothyroidism	2	1.25%		
Unexplained	10	6.25%		

Various forms of treatment were administered to these patients. 35 (58.33%) of the 60 PCO patients who received clomiphene citrate for ovulation induction became pregnant.

A combination of metformin and clomiphene citrate was administered to 20 women. 13 (65%) of them became pregnant. Gonadotrophins were given to 10 cases. 2 patients (20%) became pregnant out of them. Three (60%) of the five patients who had laparoscopic drilling became pregnant. (Table II)

TABLE 2		
Method of Treatment.	Patients treated N	Patients conceived %

clomiphene citrate	60	35 (58.33%)
Metformin+Clomiphene Citrate	20	13 (65%)
Gonadotrophins	10	2 (20%)
Laparoscopic ovarian drilling	5	3 (60%)

## DISCUSSION

According to this study, PCO-related infertility accounted for 37.5% of female factor-related infertility, making it the second most common cause. According to a study conducted to determine the prevalence of PCOS in Pakistan, it was 20.7%. 52 women with polycystic ovarian syndrome and reproductive deficit participated in this retrospective study, which was conducted at the Women Clinic and reproductive Advisory Center in Islamabad between January 1997 and May 1999. Analysis has been done on the diagnosis and treatment of these instances. The frequency of PCOS In this study, 20.7% of participants .The initial course of treatment was clomiphene citrate. The cumulative pregnancy rate with this medication is close to that of a typical woman; for example, the pregnancy rate was almost 72% when using clomiphene. A study with nearly identical findings found that women under 35 with PCOS should have a 10-15% monthly chance of becoming pregnant while taking Clomid (for roughly 3–4 months) if they are ovulating with the medication (sperm and fallopian tubes must be normal for these statistics to be valid). 20 the patient who did not respond to clomiphene citrate on its own. When metformin and clomiphene citrate were administered together, the pregnancy rate rose. Metaformin + clomiphene citrate may be better than clomiphene alone, according to a recent meta-analysis of eight randomized controlled trials. 21 The use of metformin in conjunction with clomiphene for ovulatory infertility is supported by the National Institute of Clinical Excellence's (NICE 224) guidelines in the United Kingdom. Another study found that the combination of metformin and clomiphene citrate increased the rate of pregnancy compared to using clomiphene citrate alone. Twelve According to a different study, metformin and clomiphene citrate together may raise ovulation and pregnancy rates, but they do not considerably raise the live birth rate when compared to clomiphene citrate alone. For older women with visceral obesity and clomiphene resistance, metformin may be given to clomiphene citrate. 22 About 60% of patients were conceived throughout this trial period following laparoscopic drilling (LOD), which demonstrated encouraging results. Another study that examined the safety and efficacy of mini laparotomy and ovarian drilling for subfertile women with clomiphene-resistant polycystic ovarian syndrome also produced the same findings. Within six months of ovarian drilling, 14 of 16 patients ovulated. Eleven patients were pregnant during the six-month follow-up, with a about 68.75% pregnancy rate. Young patients with secondary infertility were shown to have the highest rates of infertility, leading to the conclusion that One effective treatment for polycystic ovaries is ovarian drilling. 20 Bilateral ovarian drilling and metformin/letrozole together may be just as successful as second-line treatment for infertile women with clomiphene citrate-resistant PCOS, according to a randomized research. In this study, 73 patients had bilateral ovarian drilling, while 146 patients received letrozole and metformin. The Metformin/letrozole group showed a significant decrease in fasting insulin, testosterone, and the ratio of fasting glucose to fasting insulin. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the ratio of LH to FSH were all significantly lower in the bilateral drilling group. In terms of ovulation, pregnancy rate, abortion rate, and cycle regularity, there was no discernible difference between the patients in the two groups. 23

Another therapy option was gonadotrophins, which were taken in conjunction with close hormonal and ultrasonography monitoring to prevent ovarian hyperstimulation syndrome. Compared to other treatment modalities, particularly LOD, the conception rate was lower. However, a 2010 study notes that one must take into account the possibility that LOD could result in a reduction in ovarian reserve because of adhesion formation and surgical damage of the ovarian capsule, both of which could affect infertility. LOD must therefore continue to be a second or third-line therapeutic choice. 24 Another study found that insulin-lowering medications are safer than laparoscopic ovarian drilling in patients with clomiphene citrate resistance. It has been determined that: In PCOS patients who are resistant to CC, preference may be given to the combination of rosiglitazone and CC therapy in order to reduce the risk of ill effects of LOD. 25 According to a different study, a double-blind experiment conducted by Legro et al., letrozole works better than clomiphene to treat PCOS-related infertility. The study, which included 750 anovulatory women with PCOS, found that the birth rates for letrozole and clomiphene were 19.1% and 27.5%, respectively, based on treatment periods of up to five cycles. While the chance of twin births was decreased with letrozole, the rate of congenital malformations and the risk of pregnancy loss were found to be equivalent in the letrozole and clomiphene groups. 26 However, another study examines the reproductive outcome and hormonal-metabolic profile of PCO patients, comparing the incidence of clomiphene resistance in women on Metformin and those undergoing laparoscopic ovarian drilling. The authors came to the conclusion that while metformin is superior at reducing insulin resistance, laparoscopic ovarian drilling is linked to increased ovulation and conception rates. 27

## **CONCLUSION**

PCOS is actually a medically treatable cause of female infertility when treated appropriately in carefully chosen individuals. Weight loss, exercise, and lifestyle changes should be the first line of treatment for overweight women with polycystic ovarian syndrome (PCOS) since they have been shown to be successful in reestablishing ovulatory cycles and obtaining conception. The preferred first-line treatment for infertility caused by PCOs is clomiphene citrate. In clomiphene-resistant situations, clomiphene citrate plus metformine proved to be more beneficial than clomiphene citrate alone. Gonadotrophins are not as good as laparoscopic drilling. More work is needed in this area even if couples are unwilling to undergo lengthy monitoring because of financial difficulties or because they live in remote areas, as not all places have access to the competence needed for laparoscopic ovarian drilling.

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