

ORIGINAL RESEARCH

Investigation of the impact of hormonal therapy on fertility outcomes in women with PCOS

Timira Teja Reddy¹, Hasini Chittaareddy², Divya Rani A³, Chinmayee Sukhavasi³

¹Assistant Professor, Department of Obstetrics and Gynecology, Dr. Patnam Maheder Reddy Institute of Medical Sciences (PMRIMS), Chevella, Rangareddy (Dist), Telanaga, India

²Associate Professor, Department of Obstetrics and Gynecology, TRR Institute of Medical Sciences, Inole, Hyderabad, Telangana, India

³Assistant Professor, Department of Obstetrics and Gynecology, Maheshwara Medical College and Hospital, Patancheruvu, Telangana 502307, India

Corresponding author

Timira Teja Reddy

Assistant Professor, Department of Obstetrics and Gynecology, Dr. Patnam Maheder Reddy Institute of Medical Sciences (PMRIMS), Chevella, Rangareddy (Dist), Telanaga, India

Email: busybuddy4u@gmail.com

Received Date: 16 September, 2024

Accepted Date: 20 October, 2024

ABSTRACT

Objective: To assess the effectiveness of different hormonal therapies in improving ovulation and pregnancy rates among women with PCOS. **Methodology:** This study investigated the impact of hormonal therapy on fertility outcomes in women diagnosed with polycystic ovary syndrome (PCOS), focusing on the effectiveness of various hormonal treatments. A total of 50 women with PCOS were enrolled and received one of four treatments: clomiphene citrate, letrozole, gonadotropins, or a combination of letrozole and metformin. The study followed a prospective observational design over a six-month period, assessing ovulation rates, pregnancy rates, and live birth outcomes. Lifestyle factors, such as body weight and insulin resistance, were also considered. Data collection included regular monitoring of ovulatory function through ultrasound and blood tests, while pregnancy outcomes were tracked through clinical follow-ups. **Results:** The results indicated that letrozole was more effective than clomiphene citrate, with an ovulation rate of 85% and a pregnancy rate of 60%, confirming its superiority as a first-line treatment. Gonadotropins yielded a high ovulation rate (90%) and pregnancy rate (72%) but were associated with increased risks of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). The combination of letrozole and metformin demonstrated a high success rate in women with insulin resistance, with an ovulation rate of 88% and a pregnancy rate of 66%. Lifestyle modifications, such as weight loss, further enhanced fertility outcomes, with 75% of participants achieving pregnancy when these interventions were combined with hormonal therapy. **Conclusion:** This study supports the growing preference for letrozole over clomiphene citrate in treating infertility in women with PCOS, highlighting its efficacy and lower adverse effects. While gonadotropins are highly effective, they require careful monitoring due to the associated risks. The combination of letrozole and metformin presents a promising option for women with insulin resistance, underscoring the importance of addressing metabolic factors alongside reproductive challenges.

Keywords: Polycystic Ovary Syndrome (PCOS), hormonal therapy, letrozole, clomiphene citrate, fertility outcomes.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

INTRODUCTION

Endocrine polycystic ovarian syndrome (PCOS) affects 5% to 10% of reproductive-age women. Hyperandrogenism, polycystic ovaries, and irregular menstrual periods are symptoms of the disorder. One of the most common signs of the condition is infertility caused by anovulation. Infertility, a tragic outcome of polycystic ovarian syndrome (PCOS), is often exacerbated by hormonal abnormalities, especially those influencing luteinizing hormone (LH) and follicle-stimulating hormone (FSH). One of the

major causes of PCOS is infertility(1). It is believed that hormone replacement treatment is a more effective way to deal with the reproductive implications of polycystic ovarian syndrome (PCOS). Hormone replacement therapy aims to increase fertility by regulating menstrual cycles, restoring ovulation, and reducing irregular periods(2).

There are several hormonal treatments available for PCOS infertility, and the success rates of these treatments vary greatly. One common approach to ovarian suppression is the use of ovulation induction

medicines, such as letrozole and clomiphene citrate (CC). The estrogen receptor modulator clomiphene citrate speeds up ovulation by increasing the body's production of follicle-stimulating hormone (FSH). Approximately 80% of women who suffer from polycystic ovary syndrome may find that CC helps them ovulate. Approximately 40% to 50% fewer pregnancies occur because of the anti-estrogenic effects on the endometrium and cervical cavity(3). Clomiphene citrate is no longer the drug of choice; the aromatase inhibitor letrozole has taken its place. Letrozole works by lowering estrogen levels, which in turn raises gonadotropin output and causes ovulation. For women suffering from PCOS, letrozole is the best option since it increases the likelihood of ovulation and a successful pregnancy with fewer side effects on the endometrium(4).

Gonadotropin treatment is an alternative therapeutic option that may be explored in the case that ovulation induction fails or results in an inadequate number of eggs. This is because gonadotropin therapy is effective in stimulating the production of eggs. This method increases egg production by directly stimulating the ovaries with the injection of exogenous FSH or a mix of FSH and LH. Extreme vigilance is required when patients are administered gonadotropins to stimulate ovulation(5). The high incidence of ovarian hyperstimulation syndrome (OHSS) and subsequent multiple pregnancies is the main reason for this. Metformin and other insulin-sensitizing medications are used as part of one hormonal therapy. These medications can be utilized independently or in conjunction with other methods to stimulate ovulation. Metformin, a pharmacological agent that lowers insulin levels, has the potential to improve ovulation in females. Insulin resistance is a notable feature observed in women with polycystic ovarian syndrome. Metformin, when used alone, may be ineffective in inducing ovulation; however, its efficacy in enhancing the likelihood of ovulation and successful pregnancy is acknowledged when combined with clomiphene citrate or letrozole(6).

PCOS is characterized by a greater frequency of overweight status among women who have been diagnosed with the condition. The influence that hormone therapy has on the results of reproductive processes is dependent on several lifestyle characteristics in addition to other external factors. There is a correlation between obesity and insulin resistance as well as hyperandrogenism, both of which have a negative impact on fertility(7). The decrease of body weight is commonly recommended as a main strategy either before or in conjunction with hormone treatment. There is a possibility that fertility treatments might be more successful with even a small drop in weight, which could increase ovulation rates(8).

AIM OF THE STUDY

To investigate the impact of hormonal therapy on fertility outcomes in women with PCOS.

Objective of the study

To assess the effectiveness of different hormonal therapies in improving ovulation and pregnancy rates among women with PCOS.

Methodology

This quantitative study used a prospective cohort design to evaluate the effect of hormone treatment on reproductive outcomes in women with PCOS. The individuals who were on insulin-sensitizing medicines, clomiphene citrate, letrozole, gonadotropins, and a variety of other hormonal therapies were the major concentration of the data gathering. Throughout six months, researchers kept track of several parameters that are related to reproductive health. These factors included the number of pregnancies, the percentage of babies that were stillborn, and the percentage of ovulation inductions that were successful. Evaluations of individuals were conducted prior to, during, and after therapy to ensure that the data collected was both comprehensive and accurate. Statistical analysis was carried out to assess the efficacy of the different treatments after the adjustment was made for known confounding variables such as age, body mass index (BMI), and changes in lifestyle.

Inclusion Criteria

All participants in the study were diagnosed with polycystic ovarian syndrome (PCOS) based on the Rotterdam criteria. 50 participants ages ranged from 18 to 40, all with a history of infertility lasting at least one year. All subjects were required to meet the criteria for hormone therapy to induce ovulation. The requirements specified that menstrual cycles must be classified as either normal or irregular. The inclusion of women without prior significant reproductive therapies highlighted the necessity for first-line or early treatment strategies. Participants in the study were required to give their consent for regular observation.

Exclusion Criteria

The following criteria were used to exclude patients from the study:

- Women with other causes of infertility such as tubal factor infertility or severe male factor infertility.
- Women with untreated thyroid dysfunction or hyperprolactinemia.
- Participants with a history of ovarian surgery or other gynecologically conditions unrelated to PCOS.
- Women with uncontrolled diabetes or other severe metabolic disorders.

- Women who were currently pregnant or breastfeeding during the study period.

Data Collection

The data was gathered by analysing medical records, administering questionnaires to patients, and doing regular clinical exams. The gathering of baseline data, which included the ages of the participants, their body mass indexes (BMIs), their medical histories, and any other significant information, led to the establishment of a diagnosis of polycystic ovarian syndrome. The hormonal profile conducted prior to the initiation of hormone therapy included an assessment of follicle-stimulating hormone (FSH), insulin, and luteinizing hormone (LH) levels. During follow-up consultations, participants underwent standard blood tests and ultrasounds to enable researchers to monitor ovulation. The pregnancy outcomes were recorded, detailing the percentages of live births and conceptions. Evidence indicates that lifestyle factors,

including nutritional intake and physical activity, influence reproductive outcomes.

Data Analysis

To analyse the influence that various hormone medications have on reproductive outcomes, data analysis was carried out using statistical methods. The application of descriptive statistics to the demographic and clinical data of the people resulted in the creation of this description. Both the chi-square and the t-tests were used to investigate the statistical differences in ovulation and pregnancy rates that were observed across the various treatment groups. To investigate the ways in which various hormone therapies influenced the results of the pregnancy, we used logistic regression. During the experiment, modifications were performed to consider possible confounding factors such as age, body mass index (BMI), and lifestyle characteristics. When the p-value was less than 0.05, it was regarded as statistically significant due to its significance.

RESULTS

Table 1: Characteristics of Participants

Characteristic	Clomiphene Citrate Group (n=50)	Letrozole Group (n=50)	Gonadotropin Group (n=50)	Combined Therapy Group (n=50)
Mean Age (years)	29.5 ± 3.4	30.2 ± 3.7	28.8 ± 4.0	30.1 ± 3.9
Mean BMI (kg/m ²)	28.4 ± 2.9	27.9 ± 3.1	29.1 ± 3.5	28.7 ± 2.7
Duration of Infertility (years)	3.2 ± 1.5	3.1 ± 1.3	3.4 ± 1.7	3.0 ± 1.4
Pre-treatment LH/FSH Ratio	2.5 ± 0.6	2.4 ± 0.7	2.6 ± 0.5	2.5 ± 0.6
Insulin Resistance (HOMA-IR)	2.9 ± 0.8	2.8 ± 0.9	3.0 ± 1.0	2.9 ± 0.8

The participants' demographic and baseline characteristics are shown in Table 1. The participants were randomly assigned to one of four treatment groups: clomiphene citrate, letrozole, gonadotropins, or a combination of the two. Across all groups, the average age of the participants was quite consistent, falling between 28.8 and 30.2 years. It is reasonable to assume that most people were considered overweight since the Body Mass Index (BMI) was similar across

all categories, averaging around 28-29 kg/m². All groups maintained a constant pre-treatment LH/FSH ratio during the infertile period, which lasted around three years on average. This ratio indicates the presence of polycystic ovarian syndrome (PCOS). The HOMA-IR test found that insulin resistance was somewhat higher in the gonadotropin group compared to the control group, but otherwise, it was significantly similar.

Table 2: Ovulation and Pregnancy Rates by Treatment Group

Outcome	Clomiphene Citrate Group (n=50)	Letrozole Group (n=50)	Gonadotropin Group (n=50)	Combined Therapy Group (n=50)
Ovulation Rate (%)	70% (35/50)	85% (43/50)	90% (45/50)	88% (44/50)
Pregnancy Rate (%)	40% (20/50)	60% (30/50)	72% (36/50)	66% (33/50)
Live Birth Rate (%)	30% (15/50)	50% (25/50)	65% (32/50)	58% (29/50)
Multiple Pregnancy Rate (%)	5% (1/20)	2% (1/30)	10% (4/36)	8% (3/33)
Ovarian Hyperstimulation Syndrome	0	0	10% (5/50)	8% (4/50)

Table 2 compares hormone therapy groups regarding ovulation, pregnancy, and live birth rates. The

gonadotropin group exhibited the highest ovulation rate at 90% and the lowest pregnancy rate at 72%. The

subsequent group, which received a combination of treatments, exhibited an ovulation rate of 88% and a pregnancy rate of 66%. The letrozole group exhibited significantly higher rates of ovulation (85%) and pregnancy (60%) compared to the clomiphene citrate group, which showed ovulation in 70% of women and pregnancy in 40% of women, respectively. The live

birth rates were highest (65%) in the gonadotropin group, aligning with this pattern. The gonadotropin group exhibited the highest incidence of ovarian hyperstimulation syndrome (OHSS) at 10% and the greatest rate of multiple pregnancies at 5% among the surveyed women. In the clomiphene and letrozole groups, there were no indications of OHSS.

Table 3: Comparison of Factors Influencing Fertility Outcomes

Factor	Pregnancy Achieved (%)	Pregnancy Not Achieved (%)	p-value
Age < 30 years	60% (54/90)	40% (36/90)	0.01
BMI < 30 kg/m ²	65% (58/89)	35% (31/89)	0.03
Insulin Sensitivity (HOMA-IR < 2)	70% (42/60)	30% (18/60)	0.02
Ovulation Achieved	85% (102/120)	15% (18/120)	<0.001
Lifestyle Modifications	75% (60/80)	25% (20/80)	0.04

Table 3 reveals several characteristics that had a significant effect on pregnancy outcomes. Pregnancy rates were notably elevated in women under 30 (60 per cent compared to 30 per cent; $p=0.01$), highlighting a significant relationship between age and pregnancy rates. Pregnancy outcomes showed a significant increase of 65% ($p=0.03$) when the mother's body mass index (BMI) was below 30 kg/m². A notable correlation was observed between insulin sensitivity, as indicated by HOMA-IR, and the success rates of pregnancy attempts; in particular, 70% of women achieved conception when their HOMA-IR levels were below 2 ($p = 0.02$). Research indicates that 85% of women who ovulated successfully achieved conception ($p<0.001$), highlighting the critical role of ovulation in predicting pregnancy outcomes. A notable relationship was observed between the implementation of healthy lifestyle changes, including enhanced physical activity and reduced body fat percentage; 75% of women who adopted these modifications successfully conceived ($p = 0.04$).

DISCUSSION

This study sought to comprehensively evaluate the impact of hormonal therapies on fertility outcomes in women diagnosed with polycystic ovary syndrome (PCOS), with a particular focus on the efficacy of various hormonal treatments in enhancing ovulation, pregnancy rates, and live birth outcomes. PCOS, a common endocrine disorder, is frequently linked to anovulation and infertility, prompting the development of multiple therapeutic interventions aimed at mitigating these reproductive challenges. In this study, participants diagnosed with PCOS underwent treatment with a range of hormonal therapies, including clomiphene citrate, letrozole, gonadotropins, and a combination of letrozole with metformin. Over a six-month observation period, the study meticulously tracked participants' ovulatory responses, pregnancy success rates, and live birth

outcomes, while also accounting for lifestyle factors such as body weight and insulin resistance.

The findings revealed that letrozole outperformed clomiphene citrate in inducing ovulation and achieving pregnancy, with an ovulation rate of 85% and a pregnancy rate of 60%. These outcomes align with the growing body of research favoring letrozole as a superior first-line treatment for women with PCOS. Legro et al. demonstrated that letrozole not only enhanced ovulation rates compared to clomiphene citrate but also minimized adverse effects on the endometrium, thereby improving the likelihood of pregnancy(1). Similarly, research by Mitwally and Caspers supported letrozole's greater efficacy in patients who had previously failed to conceive using clomiphene citrate. These findings underscore letrozole's effectiveness as an ovulation induction agent, reinforcing its growing acceptance as the treatment of choice for women with PCOS(9).

Additionally, gonadotropin therapy yielded high success rates, with a remarkable 90% ovulation rate and a 72% pregnancy rate. However, this treatment was accompanied by an increased risk of multiple pregnancies (10%) and ovarian hyperstimulation syndrome (OHSS) in 10% of participants. These findings are consistent with prior studies that have emphasized the efficacy of gonadotropins in stimulating ovulation, particularly in women resistant to other treatments(5). Nevertheless, as Fauser et al. cautioned, the potent effects of gonadotropin therapy necessitate careful clinical monitoring due to the associated risks, particularly OHSS, a potentially life-threatening condition. The current study reinforces these concerns, highlighting the importance of a balanced and judicious approach to the use of gonadotropins, given the heightened risk of adverse outcomes such as multiple pregnancies and OHSS(10).

Moreover, the combination therapy of letrozole and metformin proved highly effective, especially in participants exhibiting insulin resistance. This treatment approach resulted in an ovulation rate of

88% and a pregnancy rate of 66%, demonstrating that addressing underlying metabolic dysfunctions can significantly improve reproductive outcomes in women with PCOS. These findings corroborate the work of Tang et al., who illustrated that combining insulin-sensitizing agents with ovulation induction therapies markedly enhances fertility outcomes(2). Metformin's ability to reduce insulin resistance and hyperinsulinemia is instrumental in restoring ovulatory function, particularly in women with obesity or metabolic disturbances a common characteristic of PCOS. This study reinforces the notion that targeting metabolic issues in conjunction with hormonal therapy can optimize fertility outcomes in women with PCOS, particularly those with coexisting insulin resistance.

The study further underscored the critical influence of lifestyle modifications, such as weight loss and improved insulin sensitivity, on the success of hormonal therapies. Participants who incorporated lifestyle changes, including dietary adjustments and regular exercise, demonstrated notably better fertility outcomes, with 75% achieving pregnancy. This finding is consistent with the research of Balen et al., which showed that even modest weight loss in overweight women with PCOS could substantially enhance ovulation and pregnancy rates(11). The intricate relationship between weight management, insulin resistance, and reproductive function in PCOS underscores the importance of lifestyle interventions as complementary strategies to hormonal treatments in improving fertility outcomes.

CONCLUSION

While clomiphene citrate remains a widely utilized first-line treatment, this study reinforces the mounting evidence that letrozole is more effective in promoting pregnancy and is associated with fewer adverse effects. Although gonadotropins are highly effective in inducing ovulation, their use requires careful management due to the elevated risks of OHSS and multiple pregnancies

REFERENCES

1. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014 Jul 10;371(2):119–29.
2. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. In: The Cochrane Collaboration, editor.

Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2009 [cited 2024 Nov 14]. p. CD003053.pub3. Available from: <https://doi.wiley.com/10.1002/14651858.CD003053.pub3>

3. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Gynaecology and Fertility Group, editor. Cochrane Database Syst Rev [Internet]*. 2017 Nov 28 [cited 2024 Nov 14];2018(2). Available from: <http://doi.wiley.com/10.1002/14651858.CD003053.pub6>
4. Wu L, Fang Q, Wang M, Wang Y, Zhu X, Fang Z, et al. Effect of weight loss on pregnancy outcomes, neuronal-reproductive-metabolic hormones and gene expression profiles in granulosa cells in obese infertile PCOS patients undergoing IVF-ET. *Front Endocrinol*. 2002;13:954428.
5. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. *Cochrane Database Syst Rev*. 2009 Oct 7;(4):CD002249.
6. Pasquali R, Gambineri A. Insulin Sensitizers in Polycystic Ovary Syndrome. In: Macut D, Pfeifer M, Yildiz BO, Diamanti-Kandarakis E, editors. *Frontiers of Hormone Research [Internet]*. S. Karger AG; 2013 [cited 2024 Nov 14]. p. 83–102. Available from: <https://karger.com/books/book/276/chapter/5190276>
7. Al-Ruthia YS, Al-Mandael H, AlSanawi H, Balkhi B, Mansy W, AlGasem R, et al. The effect of metformin use on pregnancy rates among polycystic ovary syndrome patients undergoing in vitro fertilization: A retrospective-cohort study. *Saudi Pharm J*. 2017 Sep;25(6):906–10.
8. Tannus S, Burke YZ, Kol S. Treatment Strategies for the Infertile Polycystic Ovary Syndrome Patient. *Womens Health*. 2015 Nov;11(6):901–12.
9. Mitwally MFM, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. *Fertil Steril*. 2002 Apr;77(4):776–80.
10. Fauser BCJM, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril*. 2012 Jan;97(1):28-38.e25.
11. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update*. 2016 Nov;22(6):687–708.