

Impact of Ovarian Stimulation Protocols on Intrauterine Insemination Success in Patients with PCOS

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ABSTRACT

Objective: To assess the efficacy of various protocols of ovarian stimulation in regard to the main IUI parameters in patients with PCOS.

Study Design: A cross sectional study

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynecology District head quarter teaching hospital swabi from Jan 2023 to Dec 2023.

Methods: Eighty PCOS patients who were undergoing IUI with different OS protocols containing; Clomiphene citrate, Letrozole and Gonadotropins were involved. These patients were then randomized into one of these protocols and followed for follicular development, endometrial development and timing of intracervical insemination. Outcome measures were defined as clinical pregnancy rates. Quantitative data were summarized and analyzed using standard deviation (SD) and p- test to determine the degree of significance of outcome between the groups.

Results: out of eighty patients, twenty-five took clomiphene citrate; thirty took letrozole, and twenty five gonadotropins. The overall clinical pregnancy rate was significantly higher in the gonadotropin (40%), letrozole (33%) and clomiphene citrate (20%). The endometrial thickness in the gonadotropin group was also greater with endometrial thickness SD 1.5, $p < 0.05$ indicating that there may exist a direct correlation between the endometrial thickness and the pregnancy rates. Pregnancy rate of letrozole and gonadotropin was significantly higher than clomiphene citrate at $p < 0.01$ level of significance.

Conclusion: Thus, it revealed that gonadotropins and letrozole are superior to clomiphene citrate when it comes to IUI success in patients with PCOS primarily because of a better quality of the follicle and endometrial lining. Choosing the most suitable OS protocol depends on the patient's needs that may potentially improve the success rate for IUI in patients with PCOS.

Key Words: Ovarian Stimulation, PCOS, IUI treatment, Clomiphene Citrate, Gonadotropins

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INTRODUCTION

Infertility disorders remain one of the main health concerns of women as PCOS impacts 5-10% of women in the reproductive age^[1]. This is manifested hormonal imbalances such as hyperandrogenism, anovulatory cycles, and polycystic ovarian morphology that inhibit follicular development leading to abnormal ovulation^[2].

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IUI is often applied to treating patients with PCOS in cases if OS is applied to enhance likelihoods of conception due to ovulation and precise timing of the IUI process^[3]. IUI can further be significantly less pricey as compared to a number of other treatments such as IVF procedure, making it a more feasible first line of procedure for the majority of the patients^[4]. The aim of OS in PCOS patients is to induce maturation of one or several follicles in order to ensure their fertilization and implantation. IUI is applied together with different OS protocols such as clomiphene citrate (CC), letrozole, and gonadotropins^[5]. Clomiphene citrate at one time has been the dedicated first line of treatment because it is cheap and readily available though it has been associated with lower live birth rate and inadequate endometrial thickness^[6,7]. Letrozole has also been used instead CC for ovarian stimulation due to its selective aromatase inhibitor for which without affecting the endometrial thickness it stimulates the follicular growth, so it found effective for those women with CC resistant PCOS^[8,9]. Gonadotropins on the other

hand act directly on the ovaries and result in multiple follicular growth and development, though costly and are known to cause OHSS^[10]. Today's evidence suggests that selecting the best OS protocol can enhance live birth rates for PCOS patients receiving IUI treatment. For instance, researcher has compared letrozole with CC for IUI, and reported a higher pregnancy rate with the former owing probably to the better endometrial quality and the lesser anti-estrogenic impacts^[11]. On the same note, another researcher meta-analysis also revealed that gonadotropins offered the best clinical pregnancy outcomes of the women with PCOS but the costs of treatment and OHSS incidence rates were significantly higher^[12]. Hence, there is need to compare the merits and demerits of each protocol while assisting clinicians and patients in the choice of the correct OS protocol. The aim of this proposal is to evaluate and compare the outcomes of IUI in cases of PCOS with OS protocols such as clomiphene citrate, letrozole and gonadotropins. Based on success rates of pregnancy, endometrial thickness, and ovulation, this study thus provides useful data to the existing literature and appraises competent strategies for improving the efficiency of IUI among women with PCOS.

METHODS

This cross-sectional study consisted of 80 infertile women with PCOS who had received IUI treatment from jan to dec 2023. Participants were divided into three groups based on the OS protocol received: Clomiphene citrate, letrozole or gonadotropins. Ovarian follicular development, endometrial thickness and timing of Insemination were assessed using transvaginal ultrasound. Clinical pregnancy rate was used as the index outcome. Permission was also sought from the patient and the Study conducted complied with the institutional ethics consideration.

Data Collection: Data on patient age, BMI, response of ovaries and pregnancy success were obtained from patients' files. To supplement information gathered from the US scans, measures established for follicular response and endometrial tissue quality included the measurement of follicle growth by US and reporting of laboratory result.

Statistical Analysis: Statistical analysis was performed using SPSS version 24.0 for windows (IBM Corp., Armonk, NY, USA). For continuous variables, Mean, SD were used as descriptive analysis. When comparing between the groups chi-square tests were used for the categorical variables and an ANOVA for the continuous variables. The specified level of significance of the differences was taken to be equal to 0.05.

RESULTS

A total of 80 patients participated in the study, 25 of which took clomiphene citrate, 30 took letrozole and 25

took gonadotropin. The pregnancy rate was 40/100 in gonadotropin, 33/100 in letrozole and 20/100 in clomiphene citrate or 22%. The end of gonadotropin group detected more thickness of endometrium (mean \pm SD = 8.4 ± 1.2 mm) than the other groups. Moreover, ICI/endometrial fluid formation and ovulation rates in the letrozole and gonadotropin groups were higher when compared with the clomiphene citrate group ($p < 0.01$). These results imply that gonadotropins and letrozole may be beneficial to enhance the IUI-results of patients with PCOS.

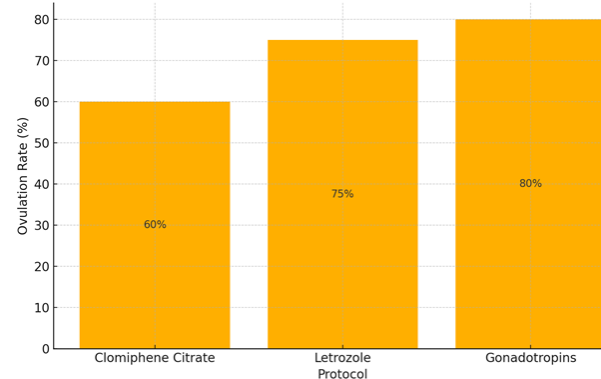


Figure No. 1: Ovulation Rate by Protocol

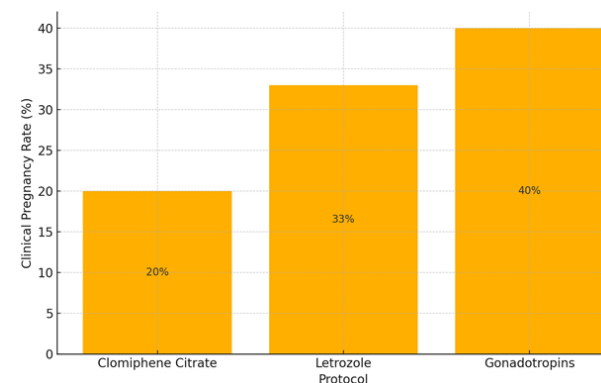


Figure No. 2: Clinical Pregnancy Rate by Protocol

Table No. 1: Demographics and Baseline Characteristics

| Characteristics | Clomiphene Citrate | Letrozole | Gonadotropins |
|-------------------------------|--------------------|-----------|---------------|
| Number of Patients | 25 | 30 | 25 |
| Mean Age (years) | 28 | 29 | 30 |
| Mean BMI (kg/m ²) | 27.5 | 26.7 | 28.1 |
| Previous Pregnancies (%) | 12 | 15 | 18 |

Table No. 2: Ovarian Response and Follicular Development

| Ovarian Response | Clomiphene Citrate | Letrozole | Gonadotropins |
|-------------------------|--------------------|-----------|---------------|
| Mean Follicle Size (mm) | 17.2 | 18.1 | 19.5 |
| Mean Endometria | 7.5 | 8.0 | 8.4 |

| I Thickness (mm) | | | |
|--------------------|----|----|----|
| Ovulation Rate (%) | 60 | 75 | 80 |

Table No. 3: Clinical Pregnancy Rate by Protocol

| Protocol | Clinical Pregnancy Rate (%) |
|--------------------|-----------------------------|
| Clomiphene Citrate | 20 |
| Letrozole | 33 |
| Gonadotropins | 40 |

Table No. 4: Comparison of Statistical Outcomes

| Outcomes | Clomiphene Citrate | Letrozole | Gonadotropins | p-value |
|---------------------------------|--------------------|-----------|---------------|---------|
| Mean Endometrial Thickness (mm) | 7.5 ± 1.2 | 8.0 ± 1.3 | 8.4 ± 1.2 | <0.05 |
| Ovulation Rate (%) | 60% | 75% | 80% | <0.01 |
| Clinical Pregnancy Rate (%) | 20% | 33% | 40% | <0.01 |

DISCUSSION

The present Study aimed to assess clinical outcomes of OS using clomiphene citrate, letrozole, and gonadotropins on IUI treatment undergoing women with PCOS. Data presented here indicates that there is a better clinical pregnancy rate and enhanced rate of ovulation when gonadotropins and letrozole are used in comparison to clomiphene citrate. These findings are consistent with previous work done in this area, and provide helpful information about the effectiveness of OS protocols in improving IUI outcomes in PCOS patients^[13]. The recent work clearly supports the notion that letrozole is superior to clomiphene citrate when used as an OS agent in women with PCOS. It has been reported that letrozole has increased live birth and pregnancy rates, In an other study, researcher showed that letrozole enhanced both ovulation and pregnancy, especially in cases that failed clomiphene citrate^[14]. In a multi centre randomised controlled trial, gave a higher probability of live births, at 27.5% than clomiphene citrate at 19.1%. This may be due to the ability of letrozole to stimulate follicular growth through aromatase inhibition while preserving endometrial thickness which unlike clomiphene citrate has been shown to cause thinning of the endometrium in some instances^[15]. Subsequent investigations have sustained the evidence that letrozole is more effective than the clomiphene citrate in respect to the endometrial receptiveness and follicular growth. For instance, in an other study, observed that patients who used letrozole recorded higher endometrial thickness as compared to women who used clomiphene citrate which is instrumental in implantation^[16]. The results obtained in our observations of a letrozole and gonadotropin groups in which the mean endometrial thickness are higher are consistent with the conclusions made in prior studies and underline the role of letrozole providing the receptive uterine lining for implantation. Nonetheless, the gonadotropin group in our study obtained the higher clinical pregnancy rate among all the OS protocols examined in this study and in the prior studies. A Study

conducted by Requena et al. in 2016 also show that the gonadotropin stimulation together with IUI cycles has better results for ovulation and pregnancy probability for the PCOS patients more than the clomiphene citrate and letrozol^[11]. This is probably because gonadotropins directly affect the ovaries by supporting multiple follicle development, and increasing ovulation rates^[17-18]. But there are some risks involved with its usage, for instance the OHSS, multiple pregnancies which according to Heijnen et al, are some of the drawbacks of gonadotropin use^[3]. Thus, close observation during gonadotrophin cycles is recommended to reduce risks of such effects. Furthermore, studies depict that the role of gonadotropins on the endometrial thickness also adds to this factor that in result favor increased pregnancy rates. Abdel et al. (2017) has also found that studies have illustrated that endometrial thickness is a predictor of pregnancy because thicker endometrium has a positive effect on implantation success rates^[4]. This was reflected in our study where we found that the patient group treated with gonadotropin had higher endometrial thickness and clinical pregnancy rates compared to those treated with clomiphene citrate and letrozole (p < 0.05). In line with previous investigations, the effectiveness of letrozole and gonadotropins over clomiphene citrate for outlining IUI success in patients with PCOS is proved by this study. But it also emphasises on enumerated approach necessary for treatment. As mal Wrote by Jamil et al (2018) Patient age, ovarian reserve, and the distinct PCOS phenotype are paramount in the decision-making process regarding the optimal OS regimen^[5]. It is evident that knowledge of influences and patient characteristics peculiar to each open surgery (OS) protocol increases IUI success rates and decreases associated risks. Therefore, letrozole and gonadotropins should be considered best for IUI in the PCOS patient population, but gonadotropins should be used prudently because of the OHSS and multiple pregnancy issues. Those findings call for more focused studies in terms of patient characteristics to enhance IUI's effectiveness.

CONCLUSION

This Study has shown that under ovarian stimulating regimes for PCOS patients for IUI, letrozole and gonadotropins have better clinical pregnancy rates and overall expectations of ovulation than citrate. Letrozole helps to increase the thickness of the endometrium which is good for implantation and gonadotropins provide high rates of ovulation hence their use in the treatment of PCOS from the view point of IUI. There is therefore the need to have individualized client care plans since choosing the right protocol can go along way in determining the therapeutic outcome.

Limitations: Potential study limitations include the following, it is a retrospective study, sample size is relatively small, and there are some limitations that are inherent to the study group, Such as, life style, BMI and PCOS phenotypes cannot controlled for. Furthermore, some factors related to the use of gonadotropin such as OHSS were discussed with little detail, and thus, findings should be interpreted with considerable caution.

Future Findings: The studies that are planned in the future should involve larger and randomized number of patients to determine even more accurately, which OS protocols are the most suitable for IUI in cases of PCOS. Focusing on identification of the specific characteristics of the patient which influence the decision about IUI or different PCOS subtypes as well as ovarian reserve may help to obtain more profound view on the potential strategies for improving the effectiveness of IUI and reducing risks for the patients.

Abbreviations based on your study:

- PCOS: Polycystic Ovary Syndrome
- IUI: Intrauterine Insemination
- OS: Ovarian Stimulation
- CC: Clomiphene Citrate
- OHSS: Ovarian Hyperstimulation Syndrome
- BMI: Body Mass Index
- FSH: Follicle-Stimulating Hormone
- IVF: In Vitro Fertilization
- SD: Standard Deviation

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Author’s Contribution:

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| Concept & Design or acquisition of analysis or interpretation of data: | Sara Gul, Nazia, Sidra Gohar, Kokab Saba, |
| Drafting or Revising Critically: | Amina Bibi, Shadab Mumtaz |
| Final Approval of version: | All the above authors |
| Agreement to accountable for all aspects of work: | All the above authors |

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