Randomised Controlled Trial

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A randomized controlled trial comparing pioglitazone and metformin prior to in vitro fertilization in polycystic ovary syndrome – associated infertile women: impact on pregnancy rates

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Background: Polycystic ovarian syndrome (PCOS) is one of the significant causes of infertility. Impaired glucose metabolism and insulin resistance add chiefly to the pathogenesis of PCOS. This study aimed to evaluate the efficacy of metformin and pioglitazone (insulin sensitizers) on the quality of the ovum and pregnancy rate in the IVF cycle.

Methods: In this randomized clinical trial study, 172 infertile women with PCO were enrolled and randomly assigned to receive either 15 mg pioglitazone (case group) or 1000 mg metformin (control group) twice a day for 6 weeks before IVF, and the pregnancy rate was compared across the groups. The number of ovum and embryos were also accessed and compared between the two groups.

Results: In the study, 172 patients participated. The mean age in the control and case groups was 32.09 ± 3.9 years and 32.12 ± 3.9 years, respectively, with no significant age difference. In both groups, the mean number of IVF eggs retrieved was 11.76 ± 3.7 (control) and 11.86 ± 3.7 (case), and the number of embryos formed was 7.43 ± 2.8 (control) and 7.87 ± 3.5 (case), with no significant disparities ($P < 0.05$). Regarding positive pregnancies, 28 out of 86 (32.6%) occurred in the control group, while 42 out of 86 (48.8%) happened in the case group, demonstrating a significant difference ($P = 0.03$).

Conclusions: According to the results obtained in this study, it may be concluded that pioglitazone is superior to metformin in IVF cycles in PCOS-associated infertile women leading to a higher pregnancy rate.

Keywords: infertile, IVF, metformin, PCOS, pioglitazone, pregnancy

Introduction

Polycystic ovary syndrome (PCOS) is a common multifaceted disease that is reported in 5–20% of women in their reproductive age[1]. Common presentations of PCOS include anovulatory cycle signs, elevated levels of serum androgens such as hirsutism and inflammatory acne, and infertility. It is seen in four different phenotypes and its diagnosis is based on Rotterdam and NIH criteria[2]. Patients with PCOS who have infertility present many complications related to the controlled ovulation stimulation cycle. Increased LH (luteinizing hormone) secretion and hyperandrogenism are associated with decreased oocyte quality, decreased ovulation, and pregnancy, as well as increased abortion.

Pathogenesis of PCOS includes genetic, environmental, and transgenerational factors. Metabolic disorders and obesity are two very common manifestations of PCOS along with reproductive and obstetric problems. Dyslipidemia, diabetes mellitus type 2, cardiovascular disease, and impaired glucose tolerance are common metabolic disorders due to PCOS. Impaired glucose tolerance including diabetes mellitus can be seen in all the phenotypes[3].

HIGHLIGHTS

- Polycystic ovarian syndrome (PCOS) is one of the significant causes of infertility.
- Impaired glucose metabolism and insulin resistance add chiefly to the pathogenesis of PCOS.
- It may be concluded that pioglitazone is superior to metformin in IVF cycles in PCOS-associated infertile women leading to a higher pregnancy rate.

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Insulin resistance also plays a role in infertility. Insulin resistance is a condition where the body's cells become resistant to the hormone insulin, which regulates blood sugar levels. This can lead to an increase in blood sugar levels and the development of conditions such as diabetes. Insulin resistance can contribute to infertility through a combination of factors including obesity, inflammation, and hormone imbalances. In lean women without PCOS, insulin resistance has been found to adversely affect IVF outcomes[4].

Previously, estrogen and progesterone were only used for the treatment of PCOS. Owing to the significant role of insulin resistance in the pathogenesis of the disease, clinical studies have suggested that insulin sensitizers such as metformin (dimethyl biguanide) and pioglitazone (glitazone/thiazolidinedione) are effective in treating PCOS, that is, presented with insulin resistance[5]. Metformin works mainly by reducing hepatic gluconeogenesis but also reduces intestinal glucose uptake and increases glucose uptake and intake. Treatment with metformin is commonly associated with adverse effects on indigestion, nausea, vomiting, abdominal cramps, and diarrhea, which may even necessitate discontinuation of treatment. Glitazones are PPAR-γ (peroxisome proliferator-activated receptor gamma) agonists. These receptors mediate signaling pathways that are associated with the proliferation of adipocytes and the transcription of inflammatory genes. PPAR-γ also regulates lipid metabolism in the liver[6].

The aim of this study was to evaluate the efficacy of metformin and pioglitazone in IVF and their impact on positive pregnancy outcomes. The study's findings could have practical implications for clinicians, offering insights into tailored interventions for PCOS-associated infertility, and contributing to the broader discussion on assisted reproductive techniques in the context of metabolic disorders.

Methods

In this randomized clinical trial study, to account for potential dropouts, a total of 172 participants were enrolled in the study.

The primary outcome of this study was the 'clinical pregnancy rate'. This measures the presence of a gestational sac with fetal heartbeat observed through ultrasound examination. It directly assesses the effectiveness of pioglitazone and metformin treatments in improving pregnancy outcomes during IVF for women with PCOS. In addition to the primary outcome of clinical pregnancy rate, this study includes several secondary outcomes. These secondary outcomes encompass the quantity and quality of oocytes retrieved during IVF, the number of embryos formed after fertilization, and assessments of various hormone levels, including FSH, LH, AMH, prolactin, progesterone, and estrogen.

In this double-blind randomized clinical trial (both participants and researchers were unaware of treatment allocation), patients referred to an infertility clinic were enrolled in this randomized clinical trial (Fig. 1). Patients were selected based on inclusion and exclusion criteria and written consent was obtained from the patients before entering the study. Patients aged less than 39 years, with clomiphene citrate-resistant-PCOS and one-time IVF failure, were included in the study. Patients above our targeted age, endometriosis, hydrosalpinx, more than one failed IVF, infertile semen analysis of the husband, severe malefactor requiring biopsy, and those who did not follow the medication protocol and did not consent to participate in the study were excluded. Randomization was performed using computer-generated random numbers, and patients were assigned to the pioglitazone or metformin group in a 1:1 ratio.

The IVF procedure was conducted using a standardized protocol. Both the pioglitazone and metformin groups underwent the same IVF procedure, following established guidelines. After ovarian stimulation, oocyte retrieval, and fertilization, blastocysts were graded based on the A-B-C grading system, with 'Blastocyst A' representing higher-quality embryos and 'Blastocyst B' representing lower-quality embryos. The grading was performed by experienced embryologists using established criteria to ensure consistency and accuracy. Blastocysts A, B, and AB were selected for IVF.

PCOS was diagnosed based on Rotterdam criteria[7]. Patients were randomly assigned to a case or control group. The case group was given 15 mg of pioglitazone twice a day for 6 weeks before IVF and the control group was given metformin, 1000 mg, twice daily. The effectiveness of medicine was measured by the rate of successful IVF that led to clinical pregnancy. Evidence of pregnancy was primarily identified by missed menstruation and blood tests, and, an ultrasound was performed every 6 weeks after successful implantation/pregnancy.

In this study, 'number of oocytes' refers to the count of mature oocytes (M2), and 'embryos' refers to the number of embryos with good grades suitable for freezing, specifically grades A and B. Also, the term 'pregnancy' in this context was defined as clinical pregnancy, meaning a pregnancy that includes a fetus with a detectable heartbeat (FHR).

Insulin sensitizer was discontinued upon identification of pregnancy. Lab hormone tests were conducted using a chemiluminescent immunoassay (Abbot Model Aclyon 300 auto-analyzer) using kits from Pars-Azmon (Tehran, Iran).

A checklist was used to collect the data, which was statistically analyzed using SPSS v22. Qualitative data was measured using frequency and for quantitative data mean and SD were used. Independent *t*-test, χ^2, and Fisher's exact tests were used and a significance level of $P < 0.05$ was considered.

Sample size calculation was based on following formula:

$$n = (Z\_alpha/2 + Z\_beta)^2 * [P1(1 - P1) + P2(1 - P2)]/(P1 - P2)^2.$$

where: n = Required sample size per group, Z_alpha/2 = Critical value for a two-tailed test at the 0.05 significance level (e.g. 1.96 for a 95% CI), Z_beta = Critical value for a power of 80% (e.g. 0.84 for 80% power), P1 = Estimated pregnancy rate in the metformin group, P2 = Estimated pregnancy rate in the pioglitazone group.

This study was approved by the Research Ethics Board of Shahid Beheshti University of Medical Sciences.

The work has been reported in line with the CONSORT criteria[8].

Research registration: researchregistry7327.

Results

After performing this calculation, it was determined that a sample size of 86 participants in each group would be required to achieve the desired power and detect the expected effect size. The mean

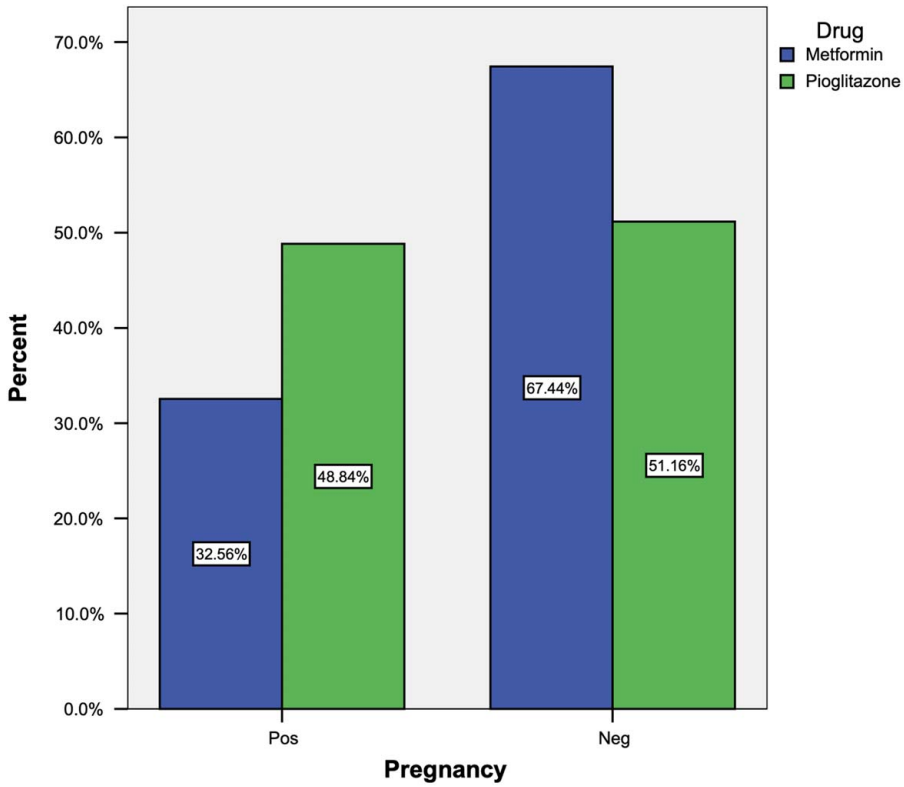

Figure 1. Flowchart of study procedures.

age of the patients in the control group was 32.09 ± 3.9 years and was 32.12 ± 3.9 years in the case group. The two groups were not significant in terms of age, $P > 0.05$ (Table 1).

Table 2 shows the levels of follicle-stimulating hormone (FSH), LH, anti-müllerian hormone (AMH), prolactin, progesterone, and estrogen in the two groups. The mean levels of these hormones were not significantly different in the two groups. The mean number of IVF eggs retrieved in the control and case groups was 11.76 ± 3.7 and 11.86 ± 3.7, respectively. The number of embryos formed in the groups was 7.43 ± 2.8 and 7.87 ± 3.5, respectively. The number of eggs retrieved, and embryos were also not significantly different, $P < 0.05$ (Table 3).

The incidence of positive pregnancy in the control group was 28 out of 86 (32.6%) and that in the case group was 42 out of 86 (48.8%). The two groups were significantly different in terms of a positive pregnancy, $P = 0.03$ (Table 4) (Fig. 2).

Discussion

Due to better tolerance of pioglitazone compared to metformin, its effectiveness in reducing inflammation, which is one of the leading causes of unsuccessful assisted reproductive techniques, and better affordability, we evaluated the effectiveness of pioglitazone in influencing the success of IVF and egg fertility. Pioglitazone reduces mortality due to cardiovascular disease and because the risk of heart disease is higher in obese and diabetic patients, it is recommended after metformin and clomiphene, which are the first line of treatment for PCOS and improvement of fertility[9]. In this study, we compared the effects of metformin and pioglitazone on IVF in PCOS women[10]. Studies have shown that metformin and pioglitazone are comparably effective for the treatment of PCOS in married and unmarried women[11]. This study is important because it focuses on comparing the effectiveness of metformin and pioglitazone in helping women with PCOS during IVF cycles. The significance lies in its potential to provide useful lessons for doctors in tailoring treatments for PCOS-related infertility.

Pioglitazone improves the endocrine status and causes inhibitory effects on androgen synthesis[12], and peroxisome proliferator-activated receptor gamma (PPAR-γ) strengthens the effect of insulin and reduces the effects of inflammation by increasing IL-8 and IL-6[13]. Upregulation of several inflammatory and downregulation of noninflammatory genes is associated with failure of IVF[14]. Evaluated the efficacy of pioglitazone for the treatment of clomiphene citrate-resistant-PCOS and controlled ovarian stimulation in IVF patients. The results of the study reported that pioglitazone reduced inflammatory markers like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the oocyte retrieved along with a greater incidence of clinical pregnancy, compared to a placebo group[15]. Pioglitazone reduces stromal blood flow and the risk of ovarian hyperstimulation and multiple pregnancies[16]. However, the treatment might

Table 1

Age distribution of patients studied

Age	Drug	Mean	SD	*P*
	Metformin	32.0930	3.92167	ns
	Pioglitazone	32.1279	3.92517	

*ns, not significant.

Table 2

Frequency distribution of laboratory values in the studied patients

	Drug	Mean	SD	P
FSH	Metformin	6.6235	5.44139	ns
	Pioglitazone	6.7042	5.43890	
LH	Metformin	5.2185	4.31438	ns
	Pioglitazone	5.2952	4.32041	
AMH	Metformin	3.4622	2.61518	ns
	Pioglitazone	3.5038	2.59096	
Prolactin	Metformin	138.2882	167.82495	ns
	Pioglitazone	136.9224	166.38413	
Progesterone	Metformin	1.7980	3.72603	ns
	Pioglitazone	14.7163	14.16266	
Estrogen	Metformin	137.0933	252.00407	ns
	Pioglitazone	130.4000	244.92678	

*ns, not significant.

Table 4

Frequency distribution of clinical pregnancies in patients

	Pregnancy			
	Positive	Negative	Total	P
Drug				
Metformin	28	58	86	0.030
	32.6%	67.4%	100.0%	
Pioglitazone	42	44	86	
	48.8%	51.2%	100.0%	
Total				
	70	102	172	
	40.7%	59.3%	100.0%	

reduce the number of oocytes retrieved for IVF[17]. Pioglitazone reduces the production of regulation upon activation of normal T-cell expressed and secreted and increases embryo implantation in endometriosis[18]. In our study, the number of embryos implantations and oocytes were not significantly different in pioglitazone and metformin groups, respectively. Nonetheless, the pioglitazone group demonstrated a notably higher count of successful pregnancies[19]. They conducted a comparative analysis of the impacts of clomiphene citrate, metformin, and pioglitazone in clomiphene citrate-resistant-PCOS women and assessed their effects on IVF outcomes.

The ovulation in the two groups was not significantly different along with conception rate and cycles. The study concluded that the efficacy of metformin and pioglitazone is similar. However, the study did not include the outcomes of pregnancy such as live birth and term birth.

In a meta-analysis conducted by Xu *et al.* (2017)[20], the comparative effectiveness of pioglitazone and metformin in treating patients with PCOS was evaluated through the analysis of multiple studies. The results of this meta-analysis suggested that pioglitazone exhibited superior outcomes in terms of improving the menstrual cycle and ovulation compared to metformin (OR = 2.31, 95% CI: 1.37–3.91, $P < 0.001$). Conversely, metformin showed a more favorable impact on BMI and F-G scores compared to pioglitazone (SMD = 0.29, 95% CI: 0.0–0.59, $P = 0.048$). Additionally, it was observed that BMI was higher in the pioglitazone group than in the metformin group (SMD = 0.83, 95% CI: 0.24–1.41, $P = 0.006$). The study concluded that pioglitazone might be a suitable alternative for PCOS patients who are intolerant or unresponsive to metformin treatment. This meta-analysis provides valuable insights into the comparative effectiveness of these two medications in managing PCOS.

Table 3

Frequency distribution of the number of ovum's and fetuses the studied patients

	Drug	Mean	SD	P
Ovum	Metformin	11.7619	3.79162	ns
	Pioglitazone	11.8690	3.72804	
Total	Metformin	12.36	4.338	ns
	Pioglitazone	12.77	5.387	
Fetus	Metformin	7.43	2.816	ns
	Pioglitazone	7.87	3.521	

ns,non-significance.

Comparing this study with ours, both studies assess the effectiveness of pioglitazone and metformin in treating PCOS-associated conditions. While our study specifically focuses on the impact of these medications on IVF outcomes and pregnancy rates in PCOS-associated infertility, the meta-analysis by Xu *et al.* evaluates a broader range of outcomes, including menstrual cycle, ovulation, BMI, and F-G scores. Despite the differences in the scope of the studies, both provide valuable insights into the use of these medications for PCOS treatment, with Xu *et al.* suggesting pioglitazone as a potential option for certain PCOS patients.

In our study, the assessment of metformin and pioglitazone efficacy in enhancing ovum quality and pregnancy rates during IVF cycles for 172 infertile women with PCOS yielded significant results. Pioglitazone demonstrated superiority over metformin, leading to a markedly higher pregnancy rate of 48.8% compared to 32.6% ($P = 0.03$). In contrast, Palomba *et al.*[21] conducted a systematic review and meta-analysis focusing on randomized controlled trials that compared metformin with placebo or no treatment in PCOS women undergoing IVF. Their findings indicated that metformin improved the clinical pregnancy rate (OR 1.62, 95% CI: 1.12–2.35) and reduced the risk of ovarian hyperstimulation syndrome (OR 0.43, 95% CI: 0.24–0.76) and miscarriage (OR 0.54, 95% CI: 0.32–0.90). Notably, our study differs from these previous investigations in several aspects, including the comparison of metformin with pioglitazone, the utilization of a higher metformin dose (2000 mg/day), the measurement of pregnancy rate as the primary outcome, and the absence of reporting on ovarian hyperstimulation syndrome or miscarriage incidences, which were key outcomes in prior studies.

The study possesses several strengths and limitations worth highlighting. One notable strength is the randomized controlled trial design, which provides a robust foundation for evaluating the comparative effectiveness of pioglitazone and metformin in IVF cycles for PCOS-associated infertility. The inclusion of substantial sample size, rigorous randomization procedures, and the assessment of various hormonal markers and clinical outcomes contribute to the study's credibility.

From the current study, pioglitazone appears to improve implantation of the developing embryo. Complete implantation

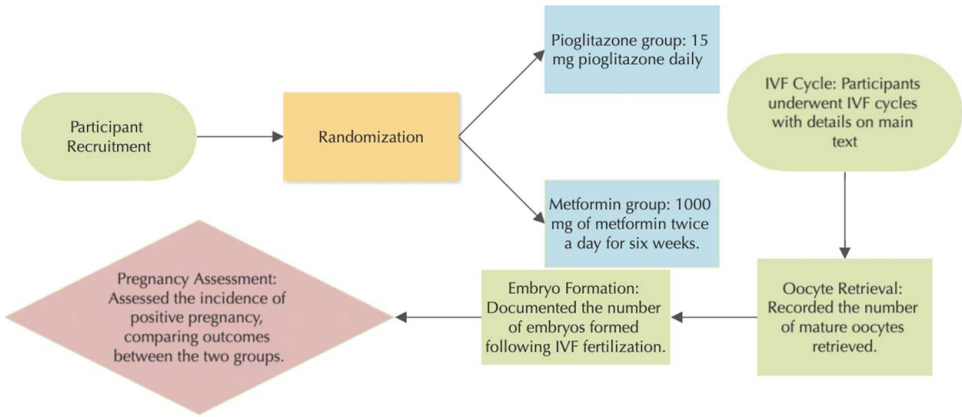

Figure 2. Frequency chart of clinical pregnancy in patients.

means pregnancy has occurred[22]. We, therefore, suggest that pioglitazone may improve the endometrium to accommodate the implanted embryo.

Study limitations

It is important to recognize some limitations in our study. Firstly, we focused on short-term outcomes during IVF cycles, so we may not fully grasp the long-term effects of using metformin and pioglitazone in women with PCOS. We also did not explore certain factors like inflammatory markers or detailed biochemical measures, which could have given a more complete picture. Additionally, we did not thoroughly examine how the medications might influence ovarian hyperstimulation, which is an important aspect of fertility treatments. Future research with longer observation periods and a broader range of factors would help overcome these limitations and provide more comprehensive insights into the use of these medications for PCOS-related infertility.

Conclusion

Based on the results obtained in this study, it may be concluded that the use of pioglitazone before IVF significantly increases the chances of achieving pregnancy compared to metformin in PCOS-associated infertile women. Nonetheless, it might not affect the number of oocytes retrieved and embryos implanted and the serum levels of androgen.

Ethical approval

This study is approved by Ethics Committee of Vice Chancellor for Research & Technology of the Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.581). All patients and control subjects signed the informed consent. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (2013) and its subsequent amendments.

Patient consent

Informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

No funding was secured for this study.

Author contribution

Dr S.N.K.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Dr R.T. and A.T.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript; Dr S.F.: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Conflicts of interest disclosures

The authors deny any conflict of interest in any terms or by any means during the study.

Research registration unique identifying number (UIN)

7327 https://www.researchregistry.com/registernow#home/registrationdetails/6182fc5fdd4451001e6f313f/.

Guarantor

Dr Seyyedeh Neda Kazemi.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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