EFFECT OF METFORMIN ON NON-POLYCYSTIC OVARY SYNDROME WOMEN UNDERGOING IVF/ICSI

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Abstract:

Background: The use of insulin-sensitising agents, such as metformin, in women who are undergoing ovulation induction or in vitro fertilisation (IVF) cycles is a valuable point of study. Metformin reduces hyperinsulinaemia and suppresses the excessive ovarian production of androgens. It is suggested that as a consequence metformin could improve assisted reproductive techniques (ART) outcomes, such as ovarian hyperstimulation syndrome (OHSS), pregnancy, and live birth rates.

Objectives:To determine the effectiveness and safety of metformin as a co-treatment during IVF or intracytoplasmic sperm injection (ICSI) in achieving fertilization.

Methods: A prospective randomized study was conducted at the Department of Obstetrics and Gynaecology located at Beni-suef University Hospital. A total of 200 patients were allocated into two groups through a random assignment process, following the necessary approval from the ethical committee and obtaining informed consent.The study participants were randomly assigned to two distinct groups. Group A: 100 Women were administered a dosage of metformin at 850 mg, twice daily, throughout the duration of ICSI cycle. The sample size for Group B was 100. Women were either not administered will metformin or were administered a placebo. Fertilization rate was to measure the outcome of using metformin.

Results:No statistically significant difference between groups regarding the mean age of participants (P = 0.07), The mean body mass index (P = 0.78). Regarding causes of infertility; in metformin group, male factor was 24.5%, tubal factor was 18%, and unexplained infertility was 57.5%. While in control group, male factor was 22%, tubal factor was 14.5%, and unexplained infertility was 63.5%. There is no statistically significant difference between groups (P = 0.44). Regarding fertilization, the mean of fertilization rate in metformin group was 7 ± 1.3 and 7.2 ± 0.86 in control group, with (P = 0.35) but has no statistically evidence of significant difference. Regarding side effects of Metformin, 11% experienced mild side effects, but no serious side effects were reported. Also none of the cases had stopped medication along the study.

Conclusions: Metformin treatment for at 850 mg, twice daily, throughout the duration of ICSI cycle significantly has no statistically evidence of significant difference regarding fertilization parameters compared with placebo.

Key words: Metformin, Non-PCO, Intracytoplasmic sperm injection, In vitro fertilization, Fertilization

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1. Introduction:

Currently, approximately 10% of couples experience challenges with reproduction, primarily attributed to environmental factors and stress. The development of assisted reproductive technology, including in vitro fertilization-embryo transfer, artificial insemination, and ovulation induction techniques, has presented significant opportunities for individuals experiencing infertility to address their reproductive challenges. Nevertheless, there have been reports indicating that IVF technology may give rise to certain adverse effects, including OHSS [1].

Since the initial documentation of successful human pregnancies resulting from the utilisation of ICSI, significant advancements have been made in refining the ICSI technique over the course of two decades. In the field of assisted reproductive technology, ICSI is predominantly employed to address three specific indications. These include cases of severe or moderate male-factor infertility, instances of low fertilisation rates or fertilisation failure in previous conventional IVF procedures, and situations characterised by unexplained infertility. ICSI is employed in cases where there is a need to enhance the rate of fertilisation and reduce instances of fertilisation failure. ICSI is useful in situations where IVF procedures result in a high rate of fertilisation failure or low fertilisation, according to the Centres for Disease Control and Prevention [2].

Extensive research has been conducted on the utilisation of insulin-sensitizing agents, such as metformin, in women undergoing ovulation induction or IVF. Metformin has been observed to effectively decrease hyperinsulinemia and inhibit the excessive synthesis of androgens in the ovaries. Therefore, it is postulated that the administration of metformin may potentially enhance the efficacy of assisted reproductive techniques (ART) by positively impacting outcomes such as OHSS, pregnancy rates, and live birth rates [3]. The aim of this study was to assess the efficacy and safety of metformin when used as a co-treatment alongside IVF or ICSI in order to ascertain its ability to facilitate fertilization outcomes.

2. Patients and methods:

The present investigation was carried out at the Department of Obstetrics and Gynaecology located at Beni-suef University Hospital.

The study participants were randomly assigned to two distinct groups. Group A: 100 Women were administered a dosage of metformin at 850 mg, twice daily, throughout the duration of the intracytoplasmic sperm injection (ICSI) cycle.The sample size for Group B was 100. Women were either not administered will metformin or were administered a placebo .The monitoring of follicular growth was conducted using transvaginal ultrasound (TVS) and measurement of serum estradiol (E2) levels .

The administration of Bhcg at a dosage range of 5000 – 10000 IU was employed to induce ovulation once a satisfactory ovarian response was achieved, characterised by the presence of at least two follicles measuring 18 – 22 mm in diameter .

The primary objective of this clinical trial was to identify the incidence of ovarian hyperstimulation syndrome (OHSS). The secondary objectives encompassed evaluating the fertilisation rate.

The inclusion criteria for this study are as follows: • Patients between the ages of 20 and 35 who have undergone in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) using a long agonist protocol. • Patients must have a history of infertility for a minimum of two years, whether it is primary or secondary infertility.

The thyroid-stimulating hormone (TSH) and prolactin levels were within the normal range.

Exclusion criteria for this study include the following: - Patients who have used metformin within the three months preceding the study. - Patients diagnosed with polycystic ovary syndrome (PCOS) based on the Rotterdam criteria. Individuals who experience medical conditions such as kidney or liver diseases The condition of severe endometriosis. Hypothalamic amenorrhea is a condition characterised by the absence of menstrual periods, which is believed to be caused by dysfunction in the hypothalamus. The condition known as associated uterine factor. In vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) techniques utilised for the purpose of sex selection.

3. Results:

In figure (1): The baseline mean age of metformin group was 28.2±3.8, while in negative control group was 29.2 ±4.5. There is no statistically significant difference between groups (P = 0.07).

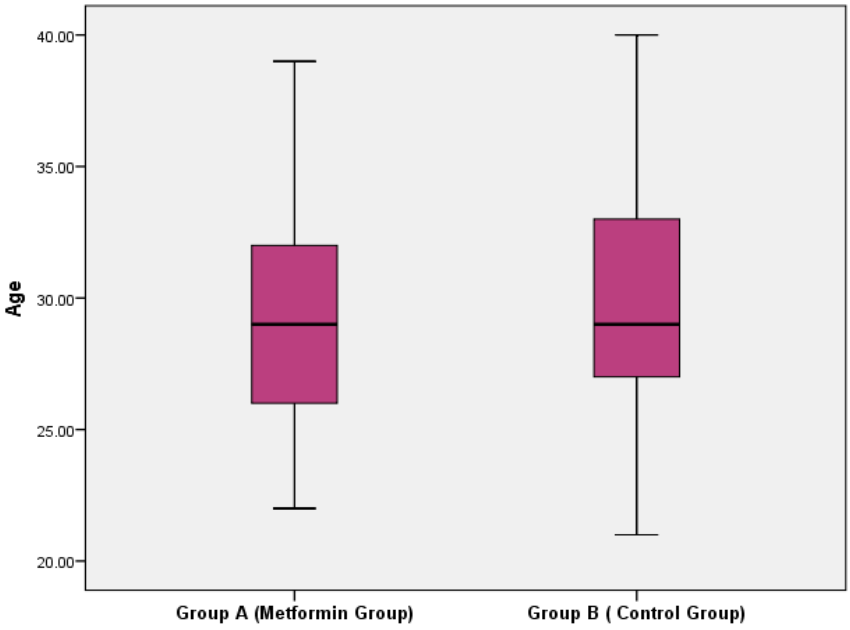

Figure (1): Age of the patients who had Metformin and control groups.

In figure (2): The mean body mass index of metformin group was 28.4 ±2.4, while the mean body mass index in negative control group was 28.6 ±1.5. There is no statistically significant difference between groups (P = 0.78).

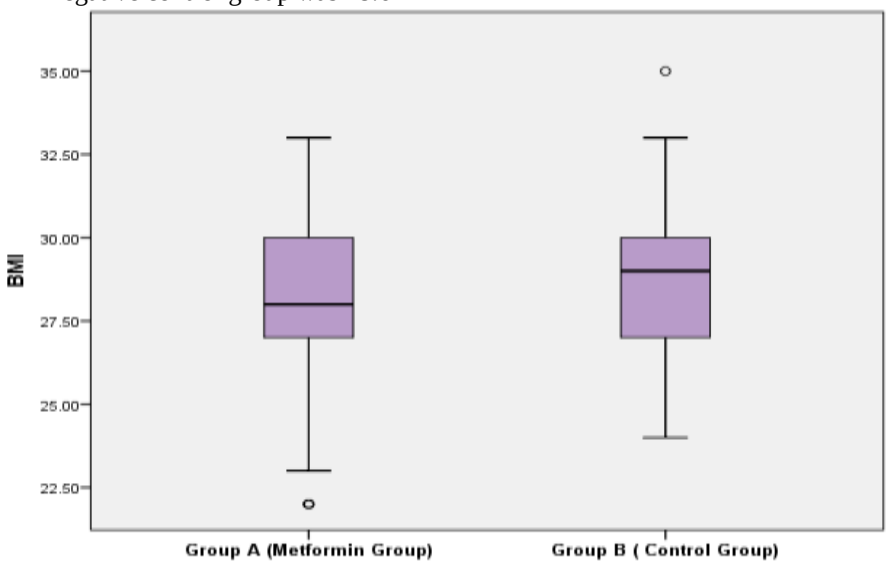

Figure (2): BMI of the patients who had Metformin and control groups.

In figure (3): Regarding causes of infertility; in metformin group, male factor was 49(24.5%), tubal factor was 36(18%), and unexplained infertility was 115 (57.5%). While in control group, male factor was 44(22%), tubal factor was 29(14.5%), and unexplained infertility was 127 (63.5%). There is no statistically significant difference between groups (P = 0.44).

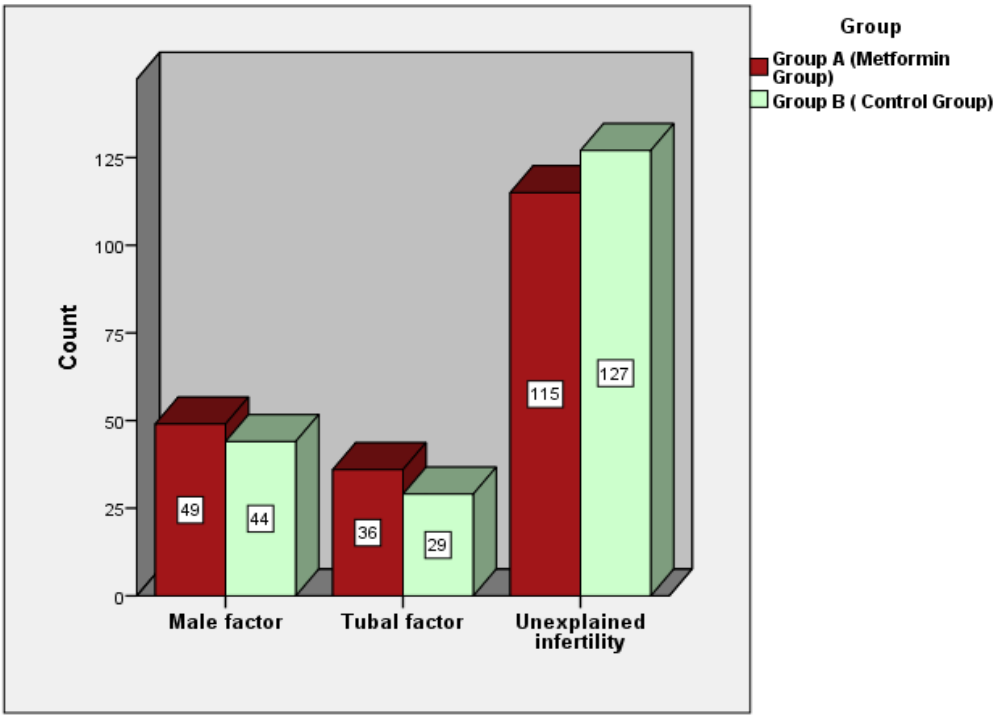

Figure (3): Cause of infertility of the patients received Metformin and control groups.

In figure (4): Regarding fertilization, the mean of fertilization rate in Group A (metformin group) was 7 ± 1.3 and 7.2 ± 0.86 in group B (control group), with (P = 0.35) which has no statistically evidence of significant difference.

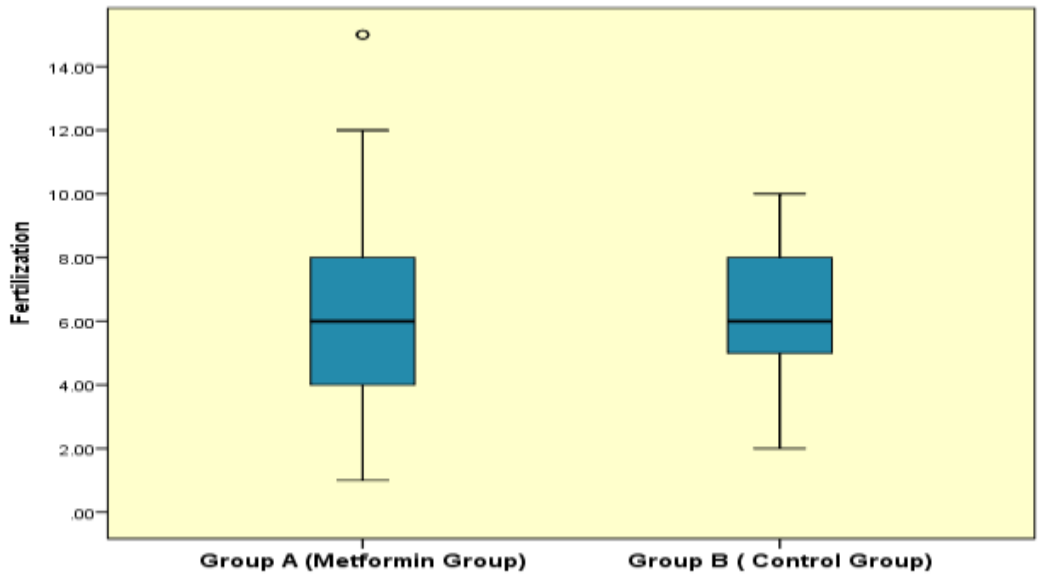

Figure (4) : Fertilization Rate among both groups.

In figure (5): Regarding side effects of Metformin, Only 22 subjects (11%) experienced mild side effects, they were mainly gastrointestinal including nausea, diarrhea and abdominal discomfort. But, No serious side effects were reported. Also none of the cases had stopped medication along the study.

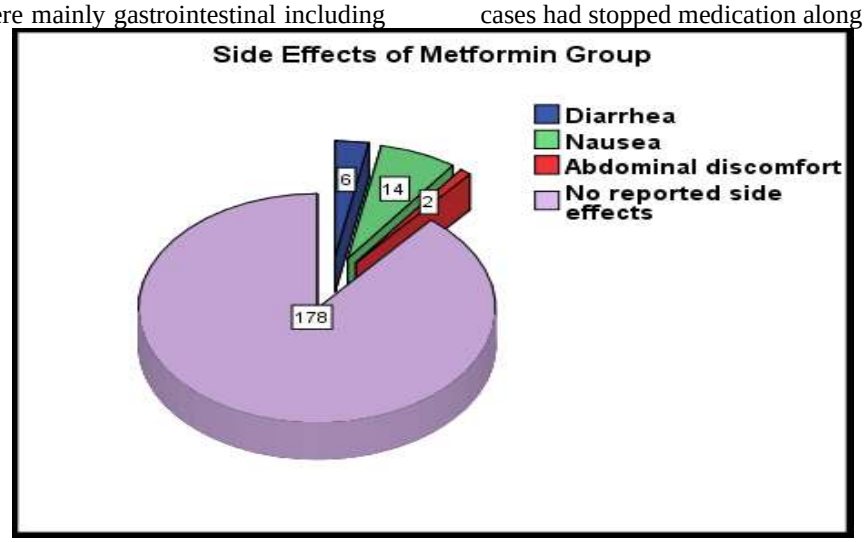

Figure (5): Side Effects reported among Group A (Metformin Group).

4. Discussion:

Metformin is commonly utilised during pregnancy, albeit with regional variations. The inclusion of metformin coadministration prior to and during ART cycle for women diagnosed with PCOS has been a common practise in numerous ART clinics, as documented by Mourad et al. [4] .

According to Nguyen et al. [5], it has been observed that metformin can be transferred from the mother to the child via the placental circulation during pregnancy. Furthermore, the concentration of metformin in foetal cord blood has been found to be similar to that in maternal blood .

It has been found that the administration of metformin does not result in a reduction in the likelihood of gestational diabetes occurrence among women who are at a higher risk for developing this condition. The consideration of metformin treatment during pregnancy should be approached with caution due to its physiological role in inhibiting cell growth and promoting programmed cell death, as highlighted by Doi et al. [6].

In the current study; the baseline mean age of metformin group was 28.2±3.8, while in negative control group was 29.2 ±4.5. There is no statistically significant difference between groups (P = 0.07). The mean body mass index of metformin group was 28.4 ±2.4, while the mean body mass index in negative control group was 28.6 ±1.5. There is no statistically significant difference between groups (P = 0.78). Regarding causes of infertility; in metformin group, male factor was 49(24.5%), tubal factor was 36(18%), and unexplained infertility was 115 (57.5%). While in control group, male factor was 44(22%), tubal factor was 29(14.5%), and unexplained infertility was 127 (63.5%). There is no

statistically significant difference between groups (P = 0.44).

In the study of Kjøtrød et al., [7], baseline demographic and disease characteristics, including age, weight and BMI, were similar in the two treatment groups. The mean age of patients was 29.5 ± 3.6 years. The majority of patients had previously received unsuccessful clomiphene citrate (CC) treatment (*n* = 59 in each treatment group). The mean number of previous cycles of CC was 3.7 ±1.8 in the metformin group and 3.5 ±1.9 in the placebo group. The metformin group experienced significant reductions in mean weight and BMI between screening and the day of oocyte collection compared with the placebo group.

Metformin according to our results; did not appear to influence fertilization rate between both groups were, (mean = 7 ± 1.3in group A and 7.2 ± 0.86 in group B) not seem to be significantly influenced with the use of metformin.

Our results are in agreement with Kjøtrød et al., [7], that, there were no significant differences between the treatments groups for any of the fertilization outcomes assessed (including the number of oocytes collected, fertilization rate and number of embryos transferred

Our results are partially in agreement with the studies of Costello et al., [8], Kjøtrød et al., [9] and Tang et al., [10].

Costello et al. [8] conducted a randomised controlled trial (RCT) to assess the efficacy of metformin as a co-treatment during IVF or ICSI in women with PCOS. The study compared metformin treatment with placebo or no treatment in PCOS patients undergoing IVF or ICSI. The findings of this study indicated that there is no evidence to support the use of metformin before or during ART cycles to improve live birth or pregnancy rates. Our study, on the other hand, included both PCOS and non-PCOS patients, unlike Costello et al.'s [8] study which specifically focused on PCOS patients. In contrast, Costello [8] observed a potential decrease in the risk of OHSS among women with PCOS who underwent IVF or ICSI cycles when treated with metformin. However, it is important to note that this particular finding could not be corroborated in our study. Additionally, Costello [8] suggested that conducting additional large RCTs is imperative in order to conclusively determine whether the administration of metformin to women with PCOS undergoing ART enhances the rates of live births and pregnancies.

In a study conducted by Kjøtrød et al. [9], the researchers examined the impact of pre-treatment with metformin on women diagnosed with PCOS who were undergoing IVF stimulation. The study involved seventy-three women with PCOS who experienced irregular or absent menstrual periods and had polycystic ovaries. These women were randomly assigned to two groups in a prospective, randomised, double-blind manner. Both groups received treatment for a minimum of 16 weeks, with one group receiving metformin (1000 mg twice daily) and the other group receiving a placebo. The treatment was discontinued on the day of human chorionic gonadotropin (HCG) injection. The researchers discovered that administering metformin before conventional IVF/ICSI in women with PCOS did not enhance stimulation or clinical outcomes. This finding aligns with the results of our study, as we included non-PCOS patients, unlike Kjøtrød's study [9], which exclusively focused on PCOS patients. However, it was observed that the administration of metformin prior to treatment showed a tendency to enhance pregnancy rates in women with PCOS who had a normal weight. However, it is important to note that our study did not provide conclusive evidence in support of this observation. Additionally, he acknowledged the necessity for additional research to be conducted on subgroups of women with PCOS.

In a study conducted by Tang et al., [10], a randomised, placebo-controlled, double-blind design was employed to investigate the impact of metformin on women with PCOS who were undergoing IVF. A total of one hundred and one IVF/ICSI cycles were randomly assigned, with fifty-two cycles receiving metformin and forty-nine cycles receiving a placebo. The findings of the study revealed that the administration of metformin alongside PCOS patients undergoing IVF/ICSI cycles led to a significant improvement in pregnancy outcomes in the short term .

Metformin not only inhibits hepatic glucose production, but also enhances insulin sensitivity, promotes peripheral glucose uptake through the induction of GLUT4enhancer factor phosphorylation, reduces the inhibitory effect of insulin on fatty acid oxidation, and decreases glucose absorption from the gastrointestinal tract. The potential cause for the heightened utilisation of glucose in the peripheral tissues could be attributed to enhanced insulin binding to insulin receptors [11].

In the current study; regarding side effects of Metformin, Only 22 subjects (11%) experienced mild side effects, they were mainly gastrointestinal including nausea, diarrhea and abdominal discomfort. But, No serious side effects were reported. Also none of the cases had stopped medication along the study.

According to Ford et al. [11], the utilisation of metformin throughout all stages of pregnancy remains a subject of contention within academic discourse. A systematic review revealed that the administration of this medication during pregnancy is associated with a decrease in the incidence of pregnancy-related complications, without any apparent adverse effects on foetal development. A separate study conducted by Butalia et al. [12] reported favourable short-term safety outcomes for

both the mother and infant. However, the long-term safety implications remain uncertain.

A total of 196 adverse effects (AEs) were reported during the study of Kjøtrød et al., [7]. Women in the metformin group experienced more AEs than those receiving placebo [overall AEs (135 versus 61), moderate/severe AEs (49 versus 13) and study drug-related AEs (76 versus 16)]. The commonly reported study drug-related AEs were nausea (metformin group, 21 patients; placebo group, 4 patients) and mild headache (metformin group, 15 patients; placebo group, 9 patients). A total of five women withdrew from the study because of an adverse drug reaction (metformin group, n = 2; placebo group, n = 3).

5. Conclusion:

Metformin treatment for at 850 mg, twice daily, throughout the duration of ICSI cycle significantly has no statistically evidence of significant difference regarding fertilization rate compared with placebo.

6. Conflict of interest:

None

6. Ethical statement:

The patients were randomly assigned to two groups after receiving approval from the ethical committee, faculty of medicine, Beni-Suef University. Prior to enrollment, all patients provided written informed consent.

7. References:

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