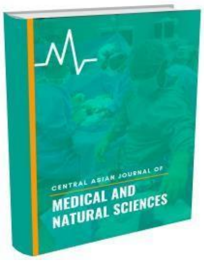

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Article

Correlation between the effect of Metformin Drug, Pregnancy Outcome, and Homo-IR in PCOS Women Undergo ICSI Technique

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Abstract: Metformin has already demonstrated its aptness in weight loss among obese women, whereas the existence of available evidence concerning the improvement in insulin resistance in PCOS women remains cloudy. The study is geared towards finding out the effect of metformin in conjunction with fresh ICSI in Iraqi women with PCOS as a potential treatment for infertility. Of the 41 referred women, most of them were diagnosed with polycystic ovary syndrome before being subjected to tests to suit the infertility clinic's facility. The study analysis was carried out using a randomized control referring to the use of forty-eight-infertile-patients with PCOS randomly assigned into two groups and before the ovarian stimulation part of the ICSI program received 500 mg of metformin treatment twice a day for some two months prior and during the ICSI cycle. A group consisting of twenty women who partaken of placebos for infertility served as the control. The basal hormonal levels are assessed at the time of the ICSI cycle: HOMA-IR was measured at the day of oocyte pickup. The main endpoints relate to the number of oocytes recovered, embryo quality, and clinical pregnancy occurrence. The number of retrieved oocytes, number of mature oocytes, peak estradiol levels, and stimulation days were similar in both groups. The study has shown that HOMA-IR is insignificantly lower in pregnant females as compared to non-pregnant females. HOMA-IR was also insubstantially lower in metformin-treated patients against control groups. There was a significant increase in pregnancy rates in metformin-treated patients (73.3% vs 26.7%; p=0.027).In conclusion, metformin therapy, either before or during ICSI cycles, significantly increases the rates of clinical pregnancy in women with PCOS. A large-scale category-wise study needs to be relied on in order to confirm the effects of metformin on the outcome of pregnancy in PCOS women undergoing the ICSI cycle because of its effect on HOMA-IR

Keywords: ICSI, PCOS, Metformin, HOMA-IR

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1. Introduction

Polycystic ovary syndrome is just one of the syndromes that cause infertility in a reproductive-age woman. According to Khan et al. (2019), polycystic ovary syndrome is a polygenic, multifactorial, autoimmune, systemic, inflammatory, and drug-dependent disease because of lifestyle changes or unhealthy habits. Irregular menses, ovarian dysfunction, and female reproductive problems are usually associated with PCOS (Falcone, T. and Hurd, W.W., 2022). In this regard, the most important cause of oligo-anovulation and hyperandrogenism in young women is PCOS, and it is usually associated with clinical and metabolic problems besides infertility (Dumesic et al., 2022). Therfore, PCOS is a complex condition with several pathophysiological mechanisms of infertility, affecting about 70% of such women (Nautiyal et al., 2022). In addition, all of these aspects would be influenced by various inputs such as genetics, pollution, and lifestyle choices, such as the time and setting.

Various theories explain the pathogenic mechanism responsible for the disorder within the clinical scope of PCOS cases. However, insulin resistance (IR) is highlighted as the most significant cause that brings about or worsens obesity for all these theories (kumar et al., 2023). The hyperinsulinemia that follows IR is responsible for stimulating ovarian androgen production, leading to PCOS development. Obesity-related inflammation also acts on ovarian physiology and insulin efficacy due to the inhibition of adipokine production (Franks S,1995). Adolescent obesity is related to increased visceral fat deposition and hormonal alterations directly affecting pituitary, hypothalamic, and ovarian function. Teenage PCOS continues to throw open a challenging clinic both for diagnosis and management. To restore ovulation, h

If all other means of ovulation induction have been exhausted, in vitro fertilization (IVF) can be considered among women with infertility due to PCOS. The process of vitro fertilization (IVF) in its initial phases involves the application of gonadotrophins to develop oocyte maturation and the production of a quality embryo that can be transferred into the recipient's uterus. However, in the overstimulation process, it also has a serious complication- ovarian hyperstimulation syndrome (OHSS). There are two methods of reducing the risk of OHSS: metformin co-treatment and low-dose gonadotrophin ovarian stimulation (Costello et al., 2020).

The major cause of this condition is the presence of insulin resistance and hyperinsuline. Thus, the common medicine provided by doctors and researchers nowadays is insulin-sensitizing drugs, which is used for the treatment of PCOS. This research aimed to find out the effects of metformin on oocyte and embryo quality as well as clinical pregnancy at ICSI in women diagnosed with PCOS, whether metformin's effects were going to bring about reductions in insulin resistance or through some different mechanisms.

2. Materials and Methods

The present cross-sectional study was conducted by recruiting 41 infertile women who were patients at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / University of Al-Nahrian between September 2022 and April 2023. The local medical ethical committee of Al-Nahrain University implements the approved study, and the patients wrote their consent to participate in the study.

Patients

The patients included in this study were selected from the patients attending the infertility clinic with the diagnosis of PCOS (n=41) and had undergone intracytoplasmic sperm injection-ICSI as a treatment. They were further classified into the following groups:

The metformin group: Twenty-one women with PCOS were treated with metformin at 500 mg twice daily during the ovarian stimulation while on ICSI Program.

Two out of three of the following criteria are from the consensus workshop group of the ESHRE/ASRMS in Rotterdam:

1) Ultrasound demonstrates polycystic ovaries.
2) Continuous oligo-or anovulation.
3) Biochemical or clinical hyperandrogenism.

Control group: Twenty infertile women with PCOS take a placebo before and during the stimulation period of preparing for the ICSI program.

Exemption criteria were women who aged less than 18 years or more than 40 years, had diabetes mellitus proven by glucose tolerance test, hyperprolactinaemia, thyroid dysfunction where medications that were discontinued affecting insulin sensitivity or immune effect only during the study duration and infectious or inflammatory disease and severe male factor infertility.

All subjects were subjected to comprehensive clinical history taking, detailed physical examination, ultrasound done to rule out polycystic ovaries, and body mass index (BMI) according to height in meters squared divided by weight in kilograms measurement, and assessment of plasma hormone levels in cycle days two or three prior to starting stimulation cycles.

According to Flegal KM. (2005), BMI is calculated by dividing weight in kilograms by height in square meters (kg/m2). Underweight is 18.5 points or less, normal weight is 18.5 points to 24.9 points, overweight is 25 points to 29.9 points, and obesity is 30 points or more (Lim JU, 2017). Venous blood sample (5 ml) was collected from each woman of two groups in cycle day 2 or 3 for baseline hormone assessment. Another sample was obtained between 8-10 am after an overnight fast at the day of ovum pickup for HOMA-IR tests.

Hormonal analysis and insulin were performed by using the TOSOH analysis apparatus through an enzyme linked fluorescent assay (ELFA) technique. The readings were done using the TOSOH leaflet kit.

The information was evaluated using Microsoft Office 2010 and SPSS version 23.0. To describe the data, descriptive statistics like frequency, range, mean, and standard deviation were computed. The groups were compared via ANOVA (for comparisons of multiple groups), independent t-test (between two groups), and chi-square (for contrasts of non-intuitive variables or proportions).

3. Results

Baseline characteristics of patients enrolled in the present study

The present cross-sectional study involved forty-one infertile females; the outcomes were presented as mean with plus minus standard deviation whereby the mean age of females was 28.76 ± 5.81 years, with a mean body mass index of 29.16 ± 5.19 and a duration of infertility equal to 7.15 ± 4.67 years. Out of these, 27 (65.9%) were primary infertility patients, and 14 (34.1%) secondary infertility patients.

Concerning the body mass indices, 8 (19.5%) were normal-weighted females, while 18 (43.9%) were overweight, and 15 (36.6%) were fat females. There were metformin prescriptions for 21 patients (51.2%), and 20 (48.8%) did not get metformin therapy (Table 1). The hormone levels, HOMA-IR, and ICSI attributes were also shown in Tables 2 and 3.

Table 1: Baseline characteristics of patients in the current study

Parameters		Range	Mean ± SD.
Age (years)		18-39	28.76 ± 5.81
BMI (Kg/m^2)		19-44	29.16 ± 5.19
Duration of infertility (years)		1 - 21	7.15 ± 4.67
BMI ranking	Normal weight	8 (19.5 %)	

	Overweight	18 (43.9 %)
	Obese	15 (36.6 %)
Type of infertility n. (%)	Primary	27 (65.9 %)
	Secondary	14 (34.1 %)
Metformin treatment	With metformin	21 (51.2 %)
	Without metformin	20 (48.8 %)

Table 2: Baseline hormonal levels of patients involved in the current study

Hormone	Range	Mean±SD
LH (mIU/ml)	1.0 – 21.0	6.35 ± 3.94
FSH (mIU/ml)	2.0 – 11.0	6.19 ± 2.14
E2 (pg/ ml)	16.0 – 94.0	45.86 ± 19.71
E2 at HCG trigger (pg/ ml)	150 – 3600	1590 ± 821
Testosterone (pg/ ml)	4.0 – 307	55.34 ± 44.46
AMH (ng/ml)	1.0 – 6.0	3.44 ± 1.35
Prolactin (ng/ml)	1.0 – 36.0	19.03 ± 9.13

TSH (mIU/ml)	1.0 – 5.0	2.00 ± 0.99
HOMA-IR (ng/ml)	0.72 – 5.06	1.77 ± 1.00

LH: Luteinizing hormone; FSH: Follicular stimulating hormone; AMH: Anti Mullerian hormone; TSH: Thyroid stimulating hormone.

Table 3: Baseline ICSI characteristics of patients involved in the current study

ICSI characteristics	Range	Mean ± SD
Total oocyte count.	1 - 24	10.95 ± 5.96
Metaphase II (MII)	1 - 17	6.49 ± 4.00
Metaphase I (MI)	0 - 8	1.63 ± 1.43
Germinal vesicles (GV)	0 - 6	0.93 ± 0.81
Abnormal oocytes	0 - 7	1.49 ± 1.29
Fertilization rate %	0 - 100	62.28 ± 20.16
Grade I embryos.	0 - 6	1.88 ± 1.55

Grade II embryos.	0 - 7	1.15 ± 0.65
Grade III embryo.	0 - 3	0.22 ± 0.18

MII: Metaphase II; MI: Metaphase I; G: Grade

Pregnancy rate of patients involved in the current study.

Out of 41 females, 15 (36.0 %) females became pregnant, 22 (54.0 %) had negative pregnancy and 4 (10.0 %) patients end with embryo freezing (Figure 1).

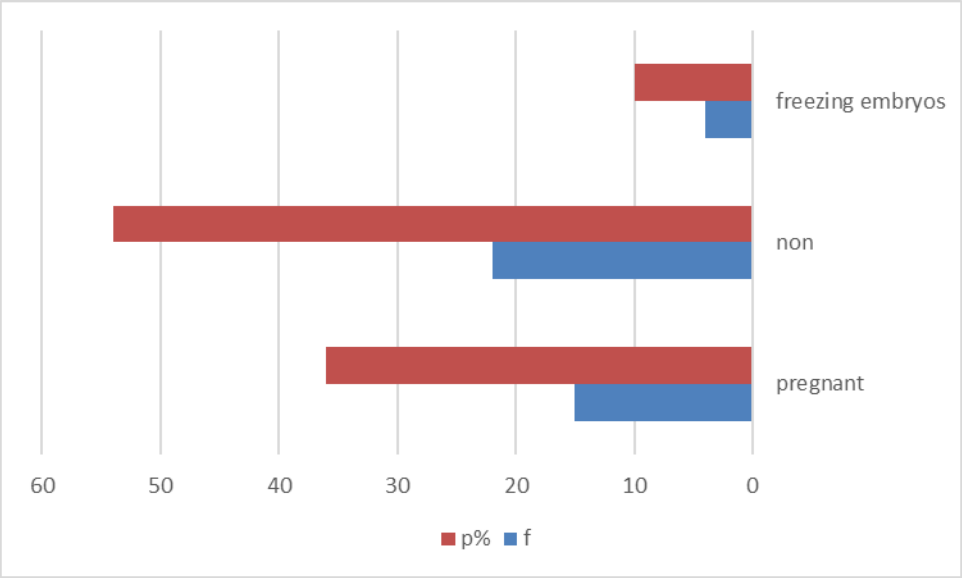

Figure 1: Pregnancy rate of patients involved in the present study.

Comparison of pregnancy rates between normal weight, overweight, and obese patients

There was an insignificantly (*p*=0.595) higher pregnancy rate in obese females (46.2 %); in addition, the pregnancy rates in normal weight and overweight patients were 25.0% and 43.8%, respectively, as demonstrated in Table 4.

Table 4: Comparison of pregnancy rates between normal weight, overweight and obese patients

Parameters	Pregnant females n.=15	Non-Pregnant females n.=22	p-value
Normal weight	2 (25.0 %)	6 (75.0 %)	0.595 € NS
Over-weight	7 (43.8 %)	9 (56.2 %)	
Obese	6 (46.2 %)	7 (53.8 %)	

N.: Numbers of patients; NS: Not significant (p> 0.05);: Chi-square

Comparison of HOMA-IR between pregnant and non-pregnant females

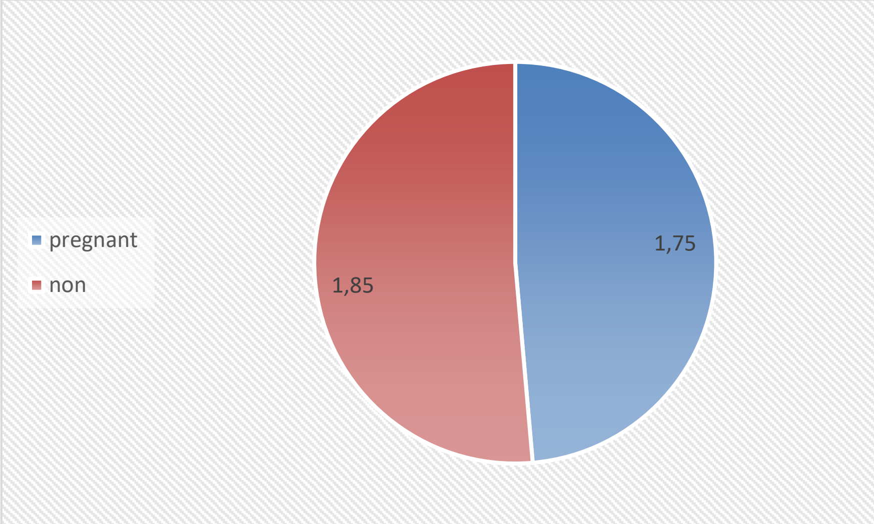

Figure 2: Comparison of HOMA-IR between pregnant and non-pregnant females, independent sample test.

Comparison of HOMA-IR between normal weight, overweight, and obese patients

There was no significant differences in HOMA-IR levels between normal-weight, over-weight, and obese females (p=0.250); the lowest mean HOMA-IR value was in normal-weight patients (1.50 ± 0.39), and the highest value in over-weight patients (2.06 ± 0.28), whilst HOMA-IR in obese patients was (1.55 ± 0.15) as demonstrated in Figure 3**.**

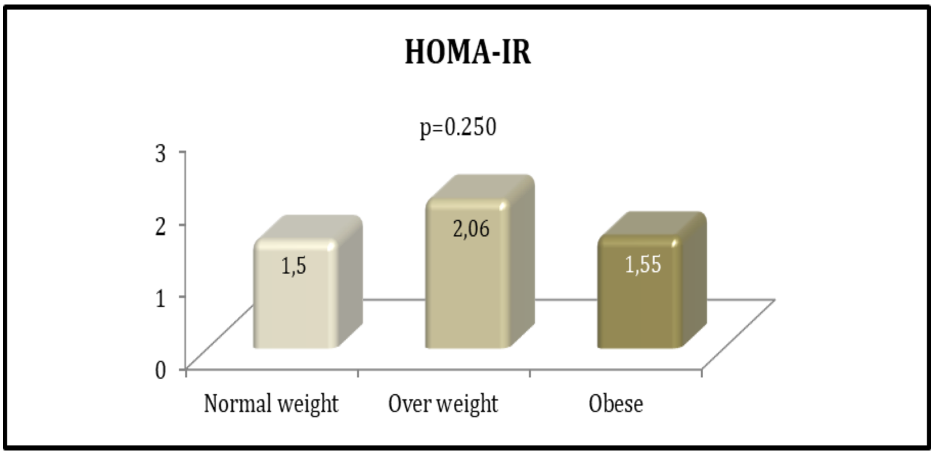

Figure 3: Comparison of HOMA-IR between normal-weight, overweight and obese patients

Comparison of positive pregnancy rates between patients with and without metformin treatment

There was significantly higher pregnancy rates in patients treated with metformin (73.3% vs. 26.7%; p=0.027), as presented in Table 5.

Table 5: Comparison of positive pregnancy rates between patients with and without metformin

Parameters	Metformin treatment N.=19	No metformin treatment N.=18	p-value
Positive pregnancy	11 (73.3 %)	4 (26.7 %)	0.027 €

Negative pregnancy	8 (36.4 %)	14 (63.6 %)	S

N.: Numbers of patients; S: Significant (p≤ 0.05);: Chi square

As in pregnancy outcomes, the number of obese patients treated with metformin was insignificantly (p=0.671) higher than normal weight and over-weight patients; 9 (60.0%) vs. 4 (50.0%) vs. 8 (44.4%) respectively, as presented in Figure 4

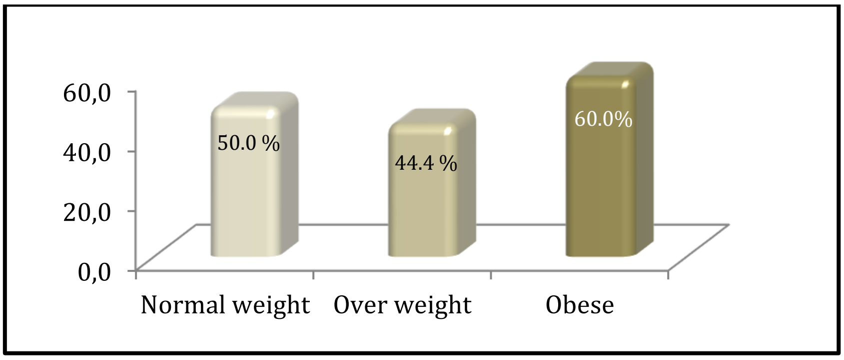

Figure 4: Percentages of normal weight, overweight, and obese patients treated with metformin€: Chi-square.

Comparison of HOMA-IR between patients with and without metformin treatment

HOMA-IR was also insignificantly lower in patients treated with metformin (1.74 ± 0.20 vs.1.79 ± 0.25; *p*=0.875), as illustrated in Table 6.

Table 6: Comparison of HOMA-IR between patients with and without metformin treatment

Parameters	Metformin treatment	No metformin treatment	p-value
HOMA-IR	1.74 ± 0.20	1.79 ± 0.25	0.875 Ŧ NS

NS: Not significant (p > 0.05); Ŧ: Independent sample t-test

Correlation between HOMA-IR with patients' clinical parameters and ICSI outcomes in both groups of patients treated and do not treat with metformin.

There were no significant correlations between HOMA-IR with patients' age, BMI, hormonal levels, and ICSI outcomes in both groups of patients treated and do not treat with metformin, as demonstrated in Table 7.

Table 7: Correlation between HOMA-IR with patients' age, BMI, and hormonal levels

Patients treated with metformin.		
Parameters	r	*p*-value
Age	0.370	0.099
BMI	0.086	0.712
LH	-0.048	0.836
FSH	0.257	0.261

E2 basal	-0.102	0.659
E2 at the day of the HCG trigger	-0.093	0.688
AMH	-0.007	0.976
Testosterone	0.067	0.771
Prolactin	0.037	0.875
TSH	-0.013	0.954
Patients do not treat them with metformin.		
Parameters	r	*p*-value
Age	0.009	0.971
BMI	-0.320	0.169
LH	0.167	0.482
FSH	0.436	0.055
E2 basal	-0.164	0.491
E2 at the day of the HCG trigger	0.242	0.319
AMH	0.142	0.550
Testosterone	-0.307	0.188
Prolactin	0.076	0.750
TSH	-0.001	0.997

r: Pearson's correlation coefficient; LH: Luteinizing hormone; FSH: Follicular stimulating hormone; AMH: Anti Mullerian hormone; TSH: Thyroid stimulating hormone.

Table 8: Correlation between HOMA-IR with patients' age, BMI, and hormonal levels

Patients treated with metformin.		
Parameters	r	*p*-value
Total oocytes	-0.018	0.939
MII oocytes	0.065	0.780
MI oocytes	-0.262	0.327
GV oocytes	-0.143	0.657
Abnormal oocytes	0.118	0.701
Fertilization rate	-0.230	0.315
GI embryos	0.336	0.262
G2 embryos	-0.125	0.731
G3 embryos	-0.310	0.690

Patients do not treat them with metformin.		
Parameters	r	p-value
Total oocytes	0.294	0.208
MII oocytes	0.174	0.464
MI oocytes	-0.430	0.125
Germinal vesicles oocytes	0.041	0.930
Abnormal oocytes	0.018	0.966
Fertilization rate	-0.013	0.957
GI embryos	0.173	0.522
G2 embryos	-0.289	0.451
G3 embryos	----	---

r: Pearson's correlation coefficient; MII: Metaphase II; MI: Metaphase I; G: Grade

4. Discussion

The prevalence of obesity is significantly higher among PCOS patients when compared to the general population (about 25%), with an obesity rate of 42-74% in PCOS patients (Azziz R,2004). The mechanisms that might be causing the association are as yet largely unproven. Previous studies have lent the argument that this condition can lead to weight gain. Resting energy expenditure appears to be normal. However, conflicting evidence exists on decreased thermogenesis (Segal KR, 1990). Altered hunger and satiety signals that may be a result of ghrelin dysregulation are also seen in this syndrome (Moran LJ, 2004).

However, in this study, the majority of patients were overweight (43.9 %), then obese and normal weight (36.6% and 19.5%), respectively. This result agrees with Gupta et al. (2019). This may be due to the random selection of cases from infertile women attending the infertility clinic whom are known to have a high prevalence of obesity regardless of whether they have PCOS or not, and the well-known association between obesity and infertility due to the higher incidence of menstrual dysfunction and anovulation (Dağ ZÖ,2014). There were no significant differences were found in the pregnancy status and HOMA-IR level. Therefore, this study indicated pregnancy outcomes after the ICSI cycle did not influence by BMI in PCOS women, and this result is similar to the result by Zhou et al. (2020).

HOMA-IR is an assay that measures the sensitivity of insulin along with the assessment of insulin resistance (Li et al., 2023). Physiologically, insulin has been said to play a part in ovarian functions as well as the maturation of oocytes; present HOMA-IR leads to decreased follicular activity (Belani et al., 2014). Many researchers indicated that HOMA-IR with 2.5 represents insulin resistance (Matthews et al. 1985) and has a negative correlation with pregnancy outcomes during ICSI cycles (Li et al. 2023). In the study, the HOMA-IR mean was 1.77, and its value was found not to associate with oogenesis, embryo development, and implantation rate in both groups: metformin treatment and control. That could probably be due to the level of HOMA-IR, which, in the case of PCO women included in this study, did not reach the threshold number, and occurred lower than 2.5.

Metformin treatment was effective in its ability to reduce oxidative stress in the follicular fluid and changes in the follicular milieu, recover a good quality and amount of oocytes and increase the number of M2 oocytes (P. Piomboni, 2014).

The study results suggest that pregnant women who are on metformin are certainly more pregnant than their counterparts. This result corroborates the work of Piomboni et al., 2014 on the beneficial effect of metformin on oocyte maturity, an area that has a strong possibility of including metformin but increases LDL-C without producing a significant effect on insulin resistance. Use of metformin might be a new strategy in lipid metabolism management in overweight and obese children and adolescents (sun et al., 2019).

Metformin co-treatment has been proposed to improve the response to exogenous gonadotropins and the success rate of assisted reproduction. There is insufficient data to determine how metformin affects the quality of oocytes or embryos; however, the metformin group demonstrated improved oocyte retrieval and clinical pregnancy rates (Tso et al. 2015).

Pregnancy complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, and neonatal morbidity, are more common in women with PCOS (Boomsma et al. 2006). Metformin may help with PCOS pregnancy outcomes, given its beneficial effects on metabolic, cardiovascular, and thrombotic events in the diabetic population (Vanky et al., 2010).

In conclusion, this study has revealed that the metformin treatment to PCOS before and during the ICSI cycle has a beneficial effect on pregnancy outcome without a significant effect on HOMA-IR and oocyte quality. This might give an idea that metformin has an indirect influence on pregnancy outcome in PCOS in the ICSI cycle.

5. Conclusion

The study titled "Correlation between the effect of Metformin drug, Pregnancy outcome, and Homo-IR in PCOS Women Undergo ICSI Technique" highlights the impact of metformin therapy on pregnancy outcomes for women with polycystic ovary syndrome (PCOS) undergoing intracytoplasmic sperm injection (ICSI). The research, conducted with 41 infertile women, aimed to evaluate metformin's effects on oocyte quality, embryo development, and clinical pregnancy rates.

Results indicate that metformin significantly improves pregnancy outcomes, with treated patients showing a clinical pregnancy rate of 73.3%, compared to 26.7% in the control group. However, the study did not find a notable effect of metformin on HOMA-IR levels or oocyte quality, suggesting its benefits may be indirect. The findings underscore metformin's potential to enhance reproductive outcomes in PCOS patients, despite its limited impact on insulin resistance within the studied population.

The authors emphasize the importance of addressing obesity and its role in PCOS-related infertility, noting that while obesity was prevalent among participants, BMI did not significantly influence pregnancy outcomes. They call for larger-scale studies to further explore metformin's mechanisms and optimize its use in fertility treatments.

In conclusion, metformin emerges as a valuable adjunct in managing PCOS-associated infertility during ICSI cycles, demonstrating a significant improvement in clinical pregnancy rates without adverse effects on insulin resistance markers or oocyte quality.

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