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Research Article

## The role of metformin in reducing rate of abortion in women with Polycystic Ovary Syndrome (PCOS)

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### ABSTRACT

The most frequent cause of anovulatory infertility globally is the result of polycystic ovary syndrome (PCOS). A lot of women with PCOS experience difficulty in getting pregnant naturally. Furthermore, when women with PCOS get pregnant they will face the risk of early pregnancy abortion as PCOS increases the risk of abortion in early pregnancy by 5 folds. This study was aimed to investigate the effect of metformin treatment in PCOS pregnant ladies compared to a control group in which metformin will not be used. The present +case-control study included 100 pregnant women who were already diagnosed to have PCOS and they were categorized into two groups, the first group included 50 women who were given metformin treatment and the second group (50 women) were given no metformin treatment in order to serve as a control group. The results of this study revealed that the rate of abortion in the study group was 9 out of 50 (18%) and this rate was significantly lower than that of the control group; 21 out of 50 (42%); ( $P=0.009$ ). Moreover, estimation of odds ratio showed that the use of metformin reduced the rate of abortion to 0.303 (95% CI of 0.121-0.756) and the preventive fraction (PF) was 0.408. Metformin is the safe and effective mode of treatment when used to reduce the rate of abortion in PCOS women.

**Keywords:** Metformin; Polycystic ovary syndrome (PCOS); Abortion.

### INTRODUCTION

The most frequent cause of an ovulatory infertility globally is the result of polycystic ovary syndrome (PCOS). A lot of women with PCOS experience difficulty in getting pregnant naturally. Furthermore, when women with PCOS get pregnant they will face the risk of early pregnancy abortion as PCOS increases the risk of abortion in early pregnancy by 5 folds (Regan *et al.*, 1990; Watson *et al.*, 1993; Nawaz *et al.*, 2008). Added to that the risk of gestational diabetes, preeclampsia, premature delivery, prenatal morbidity, and entrance to the neonatal intensive care unit (Boomsma *et al.*, 2006). The cause of early pregnancy loss in women with PCOS is still enigmatic; however, it has been postulated by some authors that insulin resistance may play a role through interference with embryo-endometrial interaction during the process of implantation, in addition it was found that insulin resistance is associated with raised androgen concentration with more destructive effect on implantation process (Carmina *et al.*, 1992; Dunaif *et al.*, 1989). On the other hand, experimental use of insulin-sensitizer

(such as metformin) was accompanied by a reduction in serum androgen concentration, re-establishment of ovulation and a significant reduction in the rate of early pregnancy abortion (Moggetti *et al.*, 2000; Al-Biate *et al.*, 2015).

Reports on the possibility of teratogenic effects when metformin used in pregnancy caused the limited use of this drug; however, studies have shown the safe use of metformin during pregnancy despite its ability to pass across placental blood barrier especially at a time of delivery (Graham *et al.*, 2011). Lack of maternal or neonatal complications was reported when metformin was used during pregnancy as an oral hypoglycemic agent (Marques *et al.*, 2014).

Despite the above data that support a beneficial role of metformin in reducing obstetric complication in pregnant women with PCOS, several studies reported contrary results and stated that metformin showed no significant effect in reducing early pregnancy loss (Vanky *et al.*, 2010). So, the presence of enough controversy about the role of metformin in pregnancy in women with PCOS permitted the conduction of the current study and the aim of the present study was to investigate the effect of metformin treatment in PCOS pregnant ladies compared to a control group in which metformin will not be used. Therefore, the issue of whether metformin treatment would help to achieve a better final outcome for both mothers and babies remains unclear.

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## PATIENTS & METHODS

The present case-control study included 100 pregnant women who were already diagnosed to have PCOS and they were categorized into two groups, the first group included 50 women who were given metformin treatment in a daily dose of 500mg and treatment continued till the end of the 12 weeks of gestation and women in the second group (50 women) serve as a control group. The study was carried out in Al-Diwaniyah child and maternity teaching hospital in Al-Diwaniyah Province/ Iraq from January 2016 until August 2017. Age, body mass index (BMI) and fasting blood sugar (FBS) were estimated at early pregnancy for all participating women. All women were followed up till term in order to record the occurrence of abortion.

### Statistical Analysis

Data were collected and transferred to SPSS (version 23) spreadsheet and analyzed and were presented as a mean and standard deviation. Independent samples t-test was used to compare mean age, BMI, and FBS between study and control groups. Chi-Square was used to study the difference in the rate of abortion between study and control groups and for risk estimation Odds ratio (OR) and etiologic fraction (EF) were estimated.

## RESULTS

The present study included 50 women with PCOS who received metformin treatment and another group of 50 PCOS women who received no treatment serving as a control group. Mean age of women in the study and control groups was 27.44 ±3.65 and 27.88 ±3.82 years, respectively and the difference was not significant (P = 0.557). Body mass index of both groups was estimated and was 26.76 ±3.70 and 27.20 ±3.82 kg/m<sup>2</sup>, respectively with no significant difference (P = 0.560). In addition, there was no significant difference in mean fasting blood glucose between study and control groups, 91.24 ±8.51 and 91.68 ±8.31 mg/dl, respectively; (P=0.794), as shown in table 1. The rate of abortion in the study group was 9 out of 50 (18%) and this rate was significantly lower than that of the control group; 21 out of 50 (42%);

(P=0.009). Moreover, estimation of Odds ratio showed that the use of metformin reduced the rate of abortion to 0.303 (95% CI of 0.121-0.756) and the preventive fraction (PF) was 0.408, as shown in table 2.

## DISCUSSION

Sohrabvand et al. (2009) tested the role of metformin on rate of abortion in women with PCOS and found that the use of metformin before pregnancy reduced the rate of abortion from 20% to 4% and that continuation of treatment for the first 8 weeks of pregnancy further reduced the rate of abortion from 40% to 8%, furthermore the continuation of treatment till 12 weeks of pregnancy caused more significant reduction in rate of pregnancy from 32% to 4% (Sohrabvand et al., 2009). This result is supportive of the finding of the present study.

In a meta-analysis carried by Zeng et al. (2016) it was found that, in 5 randomized controlled trials and eight cohort studies involving 1606 pregnant women with PCOS, the pooled odds ratio of abortion prevention was 0.19 with a confidence interval of 0.12–0.28 and highly significant effect of metformin in reducing abortion rate in early pregnancy (P<0.001) (Zeng et al., 2016) and these result are nearly similar to the results of the present study in which an odds ratio of abortion prevention was reported to be 0.303 with a confidence interval of (0.121-0.756) and significant effect of (P=0.009).

There is strong evidence that the primary pathogenesis of PCOS is accompanied by increased insulin resistance. Insulin sensitizers, including metformin, may be helpful in managing PCOS (Hag et al., 2007; Boomsma et al., 2006). There controversies about when metformin need to be discontinued and what dose of metformin should be used. Some authorities stated that discontinuation of metformin at time of pregnancy diagnosis because of fears about harms to the growing embryo (Balen et al., 2007). Even though, the proof that metformin is non-teratogenic has been reported (Boomsma et al., 2006).

Metformin half-life of is four to eight hours and it is excreted by the kidneys (Al-Biate et al., 2015). The most

**Table 1: Characteristic of study and control groups**

Characteristic	Metformin (n = 50)	No Metformin (n = 50)	P*
Age (years) (Mean ±SD)	27.44 ±3.65	27.88 ±3.82	0.557
BMI (kg/m <sup>2</sup> ) (Mean ±SD)	26.76 ±3.70	27.20 ±3.82	0.560
FBG (mg/dl) (Mean ±SD)	91.24 ±8.51	91.68 ±8.31	0.794

\*Independent samples t-test; SD: Standard deviation; BMI: Body mass index; n; number of cases

**Table 2: Association between rate of abortion and metformin treatment**

Characteristic	Metformin (n = 50)	No Metformin (n = 50)	P*	Odds ratio	95% CI	PF
Abortion	9 (81 %)	21 (42 %)	0.009	0.303	0.121-0.756	0.408
No abortion	41 (82 %)	29 (58 %)				

\*Chi-square; n: number of cases; CI: confidence interval; PF: preventive fraction

frequent side effects of metformin include gastrointestinal symptoms like nausea, vomiting, and diarrhea; nevertheless, they can be reduced or prevented by taking the treatment with a meal. The most frequent side-effects of metformin treatment were nausea and mild gastrointestinal symptoms (Hall *et al.*, 2009). Less frequent side effects include mild erythema, malabsorption of vitamin B12 and to a rare extent lactic acidosis (Lautatzis *et al.*, 2013; Dakhil, 2017).

## CONCLUSION

In conclusion, metformin is the safe and effective mode of treatment when used to reduce the rate of abortion in PCOS women.

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