

# Role of Metformin in Reducing Frequency of 1<sup>st</sup> Trimester Miscarriage among Pregnant Women with Polycystic Ovarian Syndrome at Nishtar Hospital Multan

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## ABSTRACT

**Aim:** To determine the effect of metformin in stopping miscarriage of 1<sup>st</sup> trimester among pregnant women with PCOS.

**Study Design:** Descriptive case series.

**Setting:** Antenatal clinic of Department of Obstetrics & Gynaecology, Nishtar Hospital Multan.

**Methods:** This descriptive case series was conducted from August 2010 to January 2011 at antenatal clinic of the Department of Obstetrics & Gynaecology, Nishtar Hospital Multan. The sample included 123 infertile women conceived while taking metformin. Antenatal care was given to these women at antenatal clinic of the Department of Obstetrics & Gynaecology, Nishtar Hospital Multan. The final outcome in this study was noted i.e. number of pregnancies continued in the 1<sup>st</sup> trimester while on metformin treatment and number of 1<sup>st</sup> trimester miscarriages while on metformin treatment.

**Results:** Among the 123 women who had received metformin throughout 1<sup>st</sup> trimester, there were a total of 123 pregnancies of which 12(9.8%) ended in 1<sup>st</sup> trimester miscarriage. Out of these 12 1<sup>st</sup> trimester miscarriages, 6 were at < 4 weeks, 4 at < 8 weeks and 2 were at > 8 weeks and less than 12 weeks of gestation respectively. So 112(90.2%) pregnancies remained & successfully continued in 1<sup>st</sup> trimester.

**Conclusion:** The results of this study showed that metformin usage in selected pregnant PCOS women stopped 1<sup>st</sup> trimester miscarriage in 90.2% of them. So, there should be more research trials to establish recommendation of metformin use in preventing 1<sup>st</sup> trimester miscarriage.

**Keywords:** Polycystic ovarian syndrome, hyperinsulinemia, 1<sup>st</sup> trimester miscarriage, metformin

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## INTRODUCTION

The polycystic ovarian syndrome is one of the most common endocrinopathies in women of reproductive age. It is associated with chronic anovulation, hyperinsulinemia and insulin resistance which is further aggravated during pregnancy<sup>1</sup>.

In addition to difficulty in conceiving, women with polycystic ovarian syndrome are at increased risk of miscarriage<sup>2</sup>. Rates of early pregnancy loss (1st trimester miscarriage) are reported to be 30–50% in women with polycystic ovarian syndrome which is 3-fold higher than the rate of 10–15% reported in studies for normal women<sup>3</sup>.

A key feature of PCOS is insulin resistance with compensatory hyperinsulinemia and hyperinsulinemic insulin resistance has been implicated in both the anovulation and hyperandrogenism of the disorder.<sup>4</sup> Notably, hyperinsulinemia also has been identified as an independent risk factor for 1st trimester miscarriage in PCOS<sup>5</sup>.

Metformin is a biguanide, oral hypoglycemic drug that improves tissue sensitivity to insulin, while

decreasing insulin levels and inhibiting hepatic glucose production.<sup>6</sup> When used in patients with PCOS, metformin reduces luteinizing hormone, sex hormone binding globulin and ovarian androgen and also corrects hyperinsulinemia.<sup>6,7</sup> Metformin is considered to be safe, effective and rational treatment for the metabolic and endocrine abnormalities in PCOS<sup>7,8</sup>.

The results of recent studies are reassuring that with the use of metformin, rate of first trimester miscarriage can be significantly reduced without evident teratogenicity, without intrauterine growth restriction, without maternal or neonatal side effects, without adverse effects on birth weight and height<sup>9,10,11</sup>. The purpose of this study is to observe the effect of metformin in stopping miscarriages of 1st trimester among pregnant women with PCOS.

## MATERIALS AND METHODS

This descriptive case series was conducted at antenatal clinic of the Department of Obstetrics & Gynaecology Nishtar Hospital Multan from August 2010 to January 2011 by using non probability purposive sampling technique.

A specialized proforma was developed to record findings of this study. A total 123 women with PCOS

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diagnosed on the basis of Rotterdam criteria (two out of three) 1) irregular or absent ovulation, 2) clinical or biochemical signs of hyperandrogenism like acne, hirsutism and alopecia, 3) polycystic ovaries; with 12 or more follicles measuring 2–9 mm in diameter and ovarian volume more than 10 cm<sup>3</sup> on transvaginal ultrasound and with history of previous 1<sup>st</sup> trimester miscarriage included in this study from antenatal clinics of Obstetrics & Gynecology Department of Nishtar hospital Multan. Proper permission was taken from institutional Ethical Committee to conduct this study. Informed consent was taken from each patient. This study included 123 women with PCOS, who conceived while on metformin therapy fulfilling inclusion criteria for polycystic ovarian syndrome after exclusion of other endocrinopathies. The mean dose of metformin given was 1.5gm/day throughout first trimester after confirming pregnancy by a urine pregnancy test and by detection of a gestational sac in the uterine cavity with ultrasound.

Once pregnancy was confirmed early pregnancy ultrasound evaluation repeated every fourth week. Whenever ultrasonographic evaluation suggested a poor prognosis for pregnancy outcome, or women had symptoms suggestive of miscarriage, ultrasonographic evaluation repeated. Miscarriage confirmed with ultrasound (showing empty uterine cavity).

Descriptive statistics applied to calculate mean and standard deviation for age and weight of the patients. Frequencies and percentages were calculated for two outcome variables i.e., 1) No. of pregnancies continued in the 1<sup>st</sup> trimester while on metformin treatment during current pregnancy and 2) No. of 1st trimester miscarriages among pregnant women with PCOS while on metformin treatment during current pregnancy.

## RESULTS

Among the 123 women who had received metformin throughout 1<sup>st</sup> trimester, 111(90.2%) pregnancies remained successfully in the 1<sup>st</sup> trimester and 12 (9.8%) ended in 1<sup>st</sup> trimester miscarriage. Out of these 12 1<sup>st</sup> trimester miscarriages, 6 were at <4 weeks (4.9%), 4 at <8 weeks (3.3%) and 2(1.6%) were at <12 weeks of gestation respectively. So, 111(90.2%) pregnancies successfully completed the 1<sup>st</sup> trimester.

Table 1: Outcome of patients

Outcome	n	%age
Continuation of pregnancy in 1 <sup>st</sup> trimester	111	90.2
Miscarriage at gestation <4 weeks	6	4.9
Miscarriage at gestation < 8 weeks	4	3.3
Miscarriage at gestation <12 weeks	2	1.6
Total	123	100.0

## DISCUSSION

When women with polycystic ovary syndrome finally achieve pregnancy, they are faced with the distressing prospect of a substantially increased risk for miscarriage during the first trimester<sup>3,12,13,14</sup>. The findings of this study show that decreasing hyperinsulinemic insulin resistance with metformin, in women with polycystic ovary syndrome stops 1st trimester miscarriage. When metformin was administered throughout the 1st trimester to women with the disorder, the rate of first trimester miscarriage was decreased dramatically from 41.9% to 9.75%.

The rate of first trimester miscarriage of 9.75% in the women treated with metformin is similar to the rate of 10–15% reported for clinically recognized pregnancies in normal women<sup>12,14</sup>, suggesting that metformin treatment removed any independent risk for 1<sup>st</sup> trimester miscarriage confused by the disorder itself. Moreover, results are similar to those of a pilot study, which recently reported on 1st trimester miscarriage rate of 11% in 19 women with polycystic ovary syndrome treated throughout pregnancy with metformin<sup>5</sup>.

Jahan Ara Hasan et al<sup>15</sup> in a case control interventional study comparing early pregnancy loss rate in women with polycystic ovarian syndrome, found that missed abortion rate was significantly lower (12%) in metformin group than in controls (28%) (p<0.028).

Sohrabvand et al<sup>16</sup> studied a total of 75 pregnant women with PCOS in three different groups. In Group A, metformin administration [500 mg three times daily (TDS)] was stopped immediately after diagnosis of pregnancy (5-6 weeks gestation), in Group B, metformin was administered until the end of 8 weeks gestation and in Group C until the end of 12 weeks gestation. They found a significant statistical difference between previous and current miscarriage in the current pregnancy with a decline in Group B from 40% to 8% and in group C from 32% to 4%. In spite of the reduced rate of miscarriage seen in Group A, from 20% to 4%, this difference was not statistically significant. However two RCTs conducted by Begum et al<sup>17</sup> and Morin-Papunen et al<sup>18</sup> found no difference in metformin and placebo in miscarriage rates (3.3% vs 3.3%) and (15.2% vs 17.8%) respectively.

Metformin administration may have stopped the 1<sup>st</sup> trimester miscarriage by several potential mechanisms. Elevated serum androgen concentrations have been reported to be a risk factor for 1<sup>st</sup> trimester miscarriage in the polycystic ovary syndrome.<sup>19</sup> and the women who received metformin had serum free testosterone levels, at 6-10 weeks of

pregnancy, that were 57% lower than those in the women who did not receive metformin.

Metformin's salutary effects may have been related directly to its action to improve insulin sensitivity in the polycystic ovary syndrome.<sup>5,20</sup> A recent study implicates insulin resistance as an independent risk factor for 1st trimester miscarriage in women with polycystic ovary syndrome<sup>21</sup> and a report suggests that hyperinsulinemia adversely affects endometrial function and the periimplantation environment by decreasing expression of glycodeilin and IGF binding protein-1<sup>22</sup>.

Numerous studies have demonstrated that insulin-sensitizing drugs reduce hyperinsulinemia, improve ovulation, and decrease serum testosterone concentrations in women with polycystic ovary syndrome<sup>23</sup>. However, of the commercially available drugs, only metformin has a reassuring safety profile for use during pregnancy. Metformin is classified as a category B drug. It was administered in South Africa to a limited number of women with type-2 diabetes mellitus or gestational diabetes throughout their pregnancies and no teratogenic effects or adverse fetal outcomes were reported<sup>24</sup>.

## CONCLUSION

This study showed that metformin reduced 1<sup>st</sup> trimester miscarriages to 9.75%. Prospective randomized controlled trials with sufficient number of patients are now needed to provide robust evidence to recommend the continuous use of metformin during 1<sup>st</sup> trimester among pregnant women with polycystic ovary.

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