

Role of Metformin on Recurrent Miscarriage and Other Pregnancy Complications in Women with Polycystic Ovarian Syndrome

Inaam Faisal Mohammed

Department of Obstetrics and Gynecology- College of Medicine- University of Diyala - Diyala – IRAQ

Abstract:

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Polycystic ovary syndrome signs and symptoms often begin soon after menarche. In some cases, PCOS develops later during the reproductive years, for instance, in response to substantial weight gain. The PCOS produces symptoms in about 5-10% of women of reproductive age(12-45 years) and it is one of the leading causes of female subfertility. Women with PCOS suffer not only from subfertility, but also from a high rate of early pregnancy loss. About 30-50% of clinically confirmed early pregnancy loss are associated with PCOS. In addition to early pregnancy loss, women with PCOS have increased risk of recurrent miscarriage, which defined as 3 or more consecutive pregnancy loss before 20 week. Metformin hydrochloride, an insulin sensitizing agent, has been shown to have encouraging effects on several aspect of PCOS like insulin sensitivity, plasma glucose concentration & lipid profile. It is found that using Metformin during pregnancy in women with PCOS may reduce the pregnancy loss and also reduce the risk of gestational diabetes, intrauterine growth retardation(IUGR) & preterm labor.

Aim of study: To evaluate the role of Metformin in women with recurrent miscarriage & its effect on other pregnancy complications in women with PCOS.

Patients, Materials & Methods: A prospective study done at gynecology outpatient clinic of AL-Batool Teaching Hospital in Baquba-Diyala -Iraq, from September 2012 to September 2016. A total of 100 cases were studied, all have a confirmed diagnosis of PCOS depending on the following criteria: 1) Oligo or amenorrhea (8 or fewer cycles per a year), 2) signs of hyperandrogenism 3) ultrasound features of PCOS. All should have history of 3 or more recurrent first trimester miscarriage & they were investigated for other causes of recurrent miscarriage. All cases were followed before getting pregnant and received Metformin for enhancing fertility & when they become pregnant, they were divided into two groups: the 1st group stopped using Metformin once they get pregnant while the 2nd group continued to use Metformin in a dose of 500-1000mg per day throughout pregnancy. Both groups are followed to determine pregnancy outcome.

Results: Patients who continued to receive Metformin during pregnancy had better pregnancy outcome regarding early pregnancy loss and recurrent miscarriage, gestational diabetes development, IUGR & preterm labor.

Conclusions: Metformin use during pregnancy improve pregnancy outcome in patients with polycystic ovary syndrome.

Keywords: Metformin, miscarriage, polycystic ovary syndrome.

Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Signs and symptoms often begin soon after menarche. In some cases, PCOS develops later during the reproductive years, for instance, in response to substantial weight gain ⁽¹⁾. PCOS produces symptoms in about 5-10% of women of reproductive age (12-45 years) and it is one of the leading causes of female subfertility ⁽²⁾. It is characterized by chronic anovulation & hyperandrogenism ⁽³⁾, with ultrasound features of PCOS (an ovary with 12 or more follicles measuring 2–9 mm in diameter and increased ovarian volume (>10 cm³) on transvaginal ultrasound ⁽⁴⁾. It is possible to have ovaries that are polycystic without having the typical symptoms that are in the syndrome. It is also possible to have PCOS without having multiple cysts in the ovary. The exact cause of PCOS is unknown, but may be attributed to insulin resistant, increase in luteinizing hormone, hereditary factors. Women with PCOS suffer not only from subfertility, but also from a high rate of early pregnancy loss ⁽⁵⁾. About 30-50% of clinically confirmed early pregnancy loss are associated with PCOS ⁽⁶⁾. In addition to early pregnancy loss, women with PCOS have increased risk of recurrent miscarriage, which defined as 3 or more consecutive pregnancy loss before 20 week. In previous study, PCOS women have a 2-fold increase of miscarriage after assisted reproductive technique ⁽⁷⁾. In such cases, no obvious cause of this loss is found. Several factors have been implicated as contributors to miscarriage in PCOS. These include fetal abnormalities, obesity, endometrial defect, placental thrombosis, high androgen level, increase luteinizing hormone & increase insulin resistance. Of these, insulin resistance has been considered to be the main leading cause of miscarriage in PCOS women ^(8,9). It was hypothesized that hyperinsulinemic insulin resistance contributes to early pregnancy loss in the syndrome, and that decreasing hyperinsulinemic insulin resistance during pregnancy would reduce the rate of early pregnancy loss ⁽¹⁰⁾. Metformin hydrochloride, an insulin sensitizing agent, has been shown to have encouraging effects on several aspects of PCOS like insulin sensitivity, plasma glucose

concentration & lipid profile ⁽¹¹⁾. It is found that using Metformin during pregnancy in women with PCOS may reduce the pregnancy loss and also reduce the risk of gestational diabetes & preterm labor ⁽¹²⁾.

In addition to above effects, continuous use of Metformin throughout pregnancy prevent intrauterine growth restriction. Since Metformin has no adverse effects on newborn, its use in PCOS women with pregnancy loss is encouraging ⁽¹³⁾.

Aim of study:

To evaluate the role of Metformin in women with recurrent miscarriage & its effect on other pregnancy complications in women with PCOS.

Patients, Materials & Methods:

A prospective study done at gynecology outpatient clinic of AL-Batool Teaching Hospital in Baquba-Diyala -Iraq, from September 2012 to September 2016. A total of 100 cases were studied, all have a confirmed diagnosis of PCOS depending on the following criteria: 1) Oligo or amenorrhea (8 or fewer cycles per year) 2) signs of hyperandrogenism 3) ultrasound features of PCOS. All should have history of 3 or more recurrent first trimester miscarriage & they use Metformin to enhance fertility. They were investigated for other causes of recurrent miscarriage include karyotype of both women & her husband, normal uterine anatomy confirmed by ultrasound, negative result for antiphospholipid antibodies, lupus anticoagulant & anticardiolipin antibodies IgM, IgG, with normal thyroid function & has normal 2-hour post prandial glucose.

All cases are followed before getting pregnant and received Metformin for enhancing fertility & they were divided into two groups: The 1st group stopped using Metformin once they get pregnant while the 2nd group continued to use Metformin in a dose of 500-1000mg per day throughout pregnancy

Pregnancy was confirmed by blood test for (BhcG) and then confirmed by ultrasound during first trimester & 2-hour post prandial blood glucose is done. If the patients develop any feature of miscarriage like disappearance of symptoms & signs of pregnancy ,vaginal bleeding or abdominal pain, ultrasound was done to exclude any feature of miscarriage.If non of above occurs,pregnancy followed in both groups with routine antenatal care including follow the fetal growth & wellbeing (for early diagnosis of intrauterine growth retardation or macrosomia & polyhydramnios).Blood glucose measured 2 hour post prandial during the 3rd trimester for detection of gestational diabetes.Follow up continued throughout the pregnancy & the outcome determined.

Statistical analysis

This is a prospective study. Demographic data and random blood sugar were presented as mean ± standard deviation, and the comparison between groups were done using unpaired t-test. While complications were presented as frequency and percentage and comparison between groups were done using chi square test. P value less than 0.05 was considered normal.

Results:

The results of this study shows that there was no significant difference between the two study groups (G1 discontinue Metformin when the pregnancy is confirmed,G2 continue use Metformin throughout pregnancy)regarding maternal age,body mass index(BMI) & the number of abortion at presentation ,with mean maternal age of 27.48±6.96 in G1& 26.8±6.76 in G2,the mean BMI was 26.08±7.02in G1,while it was in G2,the mean for the number of abortions was 4.44±1.28, 4.8±1.5 in G1 & G2 respectively,as shown in table1.

Table (1): Comparison of age and body mass index between group not use Metformin and group use Metformin by unpaired t test

Parameter	Not use Metformin N=50 Mean±SD	Use Metformin N=50 Mean±SD	P value
Age (yr)	27.48±6.96	26.8±6.76	0.621
BMI (kg/m ²)	26.08±7.02	26.51±6.79	0.756
No. of miscarriage	4.44±1.28	4.8±1.5	0.199

Blood glucose was not significantly different between the two groups while they were on Metformin before pregnancy (with a mean of 121.14±19.2 in G1& 120.44±16.7 in G2), but it was significantly different between the two groups during pregnancy (at 28-30week), with higher blood glucose in patients who discontinue Metformin during pregnancy with P-value <0.002 as shown in table2.

Table (2): Comparison of random blood sugar between groups not use Metformin and group use Metformin by unpaired t test

Parameter	Not use Metformin(G1) Mean±SD	Use Metformin(G2) Mean±SD	P value
RBS (mg/dl) Before pregnancy	121.14±19.2 (N=50)	120.44±16.7 (N=50)	0.846
RBS (mg/dl) At 28-30 week of gestation	155.69±37.89 (N=36)	130.95±26.82 (N=45)	0.002

The outcome of pregnancy is different between the two groups,most complications occurred more in patients who discontinue

Metformin they include: Abortion is about (10%) in patients who continue the use of Metformin versus (40%) in patients who discontinue Metformin during pregnancy. Gestational diabetes developed in 30% of patients discontinue Metformin compared to 4% in those who continue Metformin, preterm labor occurred in 12% of patients discontinue Metformin while no preterm delivery in those who continue to take Metformin. IUGR occurring in with same percentage in both groups (2%). All these findings found in table 3

Table (3): Comparison of complications between group not use Metformin and group use Metformin by Chi Square test.

Complications	Not use Metformin N=50 No. (%)	Use Metformin N=50 No. (%)	P value
Abortion	20 (40)	5 (10)	<0.001
DM	15 (30)	2 (4)	
IUGR	1 (2)	1 (2)	
Preterm labor	6 (12)	0 (0)	
None	8 (16)	42 (84)	

While complications were presented as frequency and percentage and comparison between groups were done using chi square test. P value less than 0.05 was considered normal.

Discussion:

When PCOS women lastly get pregnant after a prolong, frustrated and expensive course of fertility treatment, she will be at a substantial risk of complications, include abortion, development of gestational diabetes. Many actions had been studied to reduced these complications especially abortion so that a successful pregnancy can be achieved. One of these actions is Metformin supplementation throughout pregnancy (which was already used to improve fertility before pregnancy). Our

study on such women found that continuous use of Metformin throughout pregnancy associated with a reduction in early pregnancy loss. This finding agrees with Daniela J, Jakubwicz, Maria J *et al* 2002⁽⁶⁾ who found that Metformin use during pregnancy in women with PCOS dramatically reduce early pregnancy loss compared to those who did not use it (8.8% versus 14.9%). The same result was found in a study done by Palombas S, Falbo A, Orio F Jr *et al* 2009⁽¹⁴⁾ who conclude that the use of Metformin is effective in PCOS women with recurrent miscarriage. Glueck *et al* (2001-2002)⁽¹¹⁾, Brea Johnson (2010)⁽⁷⁾ & Paulina A. Essah, Kai I. Cheang, John E. Nestler⁽³⁾ suggest the same findings to our study.

This reduction in miscarriage rate in PCOS patients who receive Metformin is explained by the fact that insulin resistant found in PCOS patients increases during pregnancy leading to exacerbation of hyperinsulinemia found in PCOS. This hyperinsulinemia adversely affect endometrial function by reducing the expression of glycodelin & IGF-binding protein 1⁽¹⁵⁾. Glycodelin inhibit the endometrial immune response to embryo^(16, 17), while IGF-protein 1 play a role in adhesion process at fetomaternal interface^(18, 19) so Metformin as insulin sensitizer reduces hyperinsulinemia & its adverse effect on endometrium.

Metformin also reduces serum androgen concentration, as high androgen suppose to be a cause of miscarriage in PCOS⁽²⁰⁾. Also Metformin decreases the circulating plasminogen activator inhibitor-1. This inhibitor found to be increased in PCOS leading to reduction in fibrinolytic activity which considered as independent factor for miscarriage^(21, 22).

Regarding pregnancy outcome, in our study we found that both blood glucose level & the development of gestational diabetes, are lower in patients continue Metformin during pregnancy. This agrees with Khattab S, Mohsen IA, Aboulfoutouh I, *et al* (2011)⁽²³⁾. Balani

J,Hyer SL,Rodin DA,*et al*(2009)⁽²⁴⁾,Velazquez EM,Mendoza S,Hamer T,*et al*(1994)⁽²⁵⁾.They conclude that continuous use of Metformin during pregnancy in PCOS women provide a statistically significant prevention or reduction in gestational diabetes.

Preterm labor also less in patients using Metformin ,this goes with same finding found by Daniela J,Jakubowicz,Maria J eta 2002⁽⁶⁾ ,Pratp Kumar & Kashif Khan(2012)^(2) .They stated that continuous use of Metformin throughout pregnancy reduces pregnancy loss,preterm labor & intrauterine growth retardation,but in our study ,IUGR,ocurr in same percentage in both groups(use or not use Metformin)which may be due to differences in study design,or the number of patients.

Conclusions: The main conclusion of this study is the consideration of Metformin use during pregnancy improve pregnancy outcome in patients with polycystic ovary syndrome.

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