

Effects of metformin use in pregnant patients with polycystic ovary syndrome

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ABSTRACT

Use of metformin throughout pregnancy in women with polycystic ovary syndrome (PCOS) has shown to reduce the rates of early pregnancy loss, preterm labor, and prevention of fetal growth restriction. Metformin has been shown to have encouraging effects on several metabolic aspects of polycystic ovarian syndrome, such as insulin sensitivity, plasma glucose concentration and lipid profile and since women with PCOS are more likely than healthy women to suffer from pregnancy-related problems like early pregnancy loss, gestational diabetes mellitus and hypertensive states in pregnancy, the use of metformin therapy in these patients throughout pregnancy may have beneficial effects on early pregnancy loss and development of gestational diabetes.

KEY WORDS: Metformin, PCOS, pregnancy

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS produces symptoms in approximately 5 to 10% of women of reproductive age (12–45 years old) and is thought to be one of the leading causes of the female subfertility.^[1,2] PCOS is a medical condition, in which there is an imbalance of the female sex hormones i.e. elevated levels of testosterone, DHEA-S, androstenedione, prolactin, and LH along with a normal, high or low estrogen levels. According to the Rotterdam criteria,^[3] a diagnosis of PCOS can be made in a woman if she has 2 of the following 3 manifestations: Irregular or absent ovulation, elevated levels of androgenic hormones, and/or enlarged ovaries containing at least 12 follicles each. Other conditions with similar presenting signs, such as androgen-secreting tumors or Cushing's syndrome, must be ruled out before a diagnosis of PCOS is established. Controversies in continuation of metformin therapy throughout pregnancy, in women who have conceived after treatment of PCOS, has remained a controversial topic till date. This literature gives an insight into the problem.

Hyperinsulinaemia, insulin resistance and impaired glucose tolerance are very common

in women with PCOS, particularly in those with a body mass index (BMI) > 30,^[4,5] but insulin resistance may occur in lean women with PCOS. An insulin action in the ovary is mediated via the insulin receptor rather than the type 1 insulin-like growth factor (IGF) receptor, which binds IGF-I with high affinity and insulin with low affinity. Hyperinsulinaemia has shown to increase androgen production by the ovaries and hence it may play a central role in the pathogenesis of PCOS.^[6]

REVIEW OF LITERATURE

In a randomized, placebo-controlled, double blind study, done on 257 pregnant women with PCOS, aged 18 - 42 years, who either received metformin or placebo from first trimester to delivery, failed to demonstrate any reduction of pregnancy-related complications, such as gestational diabetes, pre-eclampsia and pre-term delivery in the metformin group.^[7] On the contrary, a prospective study done on 98 pregnant women with PCOS who received metformin (1700 – 3000 mg/day) before conception and up to 37 weeks of pregnancy vs. 110 normal pregnant controls, showed a significant reduction of pregnancy complications, such as gestational diabetes and gestational

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hypertension but an insignificant decrease in pre-eclampsia incidence with comparable mean neonatal Apgar scores, weight and length between the 2 groups.^[8]

Metformin has been shown to have encouraging effects on several metabolic aspects of polycystic ovarian syndrome, such as insulin sensitivity, plasma glucose concentration, and lipid profile and since women with PCOS are more likely than healthy women to suffer from pregnancy-related problems like early pregnancy loss, gestational diabetes mellitus and hypertensive states in pregnancy, the use of metformin therapy in these patients throughout pregnancy may have beneficial effects on early pregnancy loss and development of gestational diabetes. However, there is little evidence of its beneficial effect on hypertensive complications in pregnancy.^[9] In a 3-year case controlled study, conducted on 197 pregnant women with PCOS (confirmed by Rotterdam criteria), in which cases comprised of women who continued metformin throughout pregnancy while controls were women who stopped metformin after the first trimester, it was concluded that in comparison to the control group, the study group had a significant reduction in early pregnancy loss.^[10,11] Besides reducing the rates of miscarriages, continuing the use of metformin throughout pregnancy has been useful in preventing fetal growth restriction. Its use in pregnancy is devoid of any adverse effects on the new born as demonstrated by a case-controlled study, measuring pregnancy outcomes, conducted on 137 women with PCOS (Rotterdam criteria), in which there were 3 groups. The study found that the group, which continued metformin use throughout the entire pregnancy, had diminished incidences of fetal growth restriction, preterm labor, and increased live birth rates. There were also no congenital anomalies, intrauterine deaths or stillbirths reported in the test subjects, suggesting metformin use is not related to teratogenicity. Besides the above, the group which continued metformin use in the entire pregnancy had reduced incidences of early pregnancy losses and gestational diabetes.^[12]

Continuing the use of metformin during the first trimester of 66 pregnant women with PCOS, demonstrated a lower percentage of small (< 10th centile) and large (> 90th centile) for gestational age babies as compared to the 66 control groups of normal women without PCOS who did not use metformin. Neonatal hypoglycemia was also less commonly reported in the metformin group with fewer babies requiring intravenous glucose therapy.^[13] Metformin is excreted in breast milk, but the amount secreted is clinically insignificant and there have been no reported adverse effects on breastfed infants with mothers who take metformin.^[14] A study which measured growth, motor-social development and illness in 61 nursing infants (21 males and 40 females) and 50 formula-fed infants (19 males and 31 females) born to

92 mothers with PCOS who were taking metformin (median of 2.55 gm/day) throughout pregnancy and lactation, reported that none of the children had any delay in either growth or in developmental milestones.^[15]

An important link exists in patients between having an abnormal glucose tolerance test and a history of recurrent spontaneous abortions. Since women with PCOS are more prone than healthier women to have an abnormal glucose tolerance test during pregnancy, these women may also be at an increased risk of having spontaneous first trimester abortions. A prospective clinical-controlled trial concluded that metformin use in pregnant patients with an abnormal glucose tolerance test and history of recurrent spontaneous abortions effectively reduced the chances of first trimester abortion with improved chances of a successful pregnancy.^[16] Other attributed causes for miscarriages in women with PCOS are elevated levels of androgens and luteinizing hormone.^[17,18] Metformin with its favorable effects on androgen and LH levels may be useful in reducing rates of early pregnancy loss when used pre conception and continued through pregnancy.^[19] Its modification of LH levels are evident by a prospective randomized controlled trial, conducted on 32 women with PCOS with high pretreatment LH values and 32 women with normal cycles who were recruited to receive metformin (850 mg b.i.d) or placebo, for an average duration of 40 days. There was a significant reduction of LH values in PCOS women to normal baseline with metformin therapy while the FSH and TSH levels remained normal. These women also showed reduction in their prolactin levels as compared to their previous high pretreatment levels – demonstrating the effect of Metformin on the pituitary.^[20] Contrary to the results of the above-mentioned study, meta-analysis of 17 randomized controlled trials found that metformin use before conception does not reduce abortion risk in women with PCOS.^[21]

Women with polycystic ovaries are more insulin-resistant than weight-matched women with normal ovaries. An insulin resistance is seen in 10 – 15% of slim and 20 – 40% of obese women with PCOS, and women with PCOS are at increased risk of developing type 2 diabetes.^[22] Obesity has a profound adverse effect on the likelihood of a healthy pregnancy. Obesity can negatively influence chances of conception, response to fertility treatment as well as increase risks of miscarriages and congenital anomalies along with increasing the risks for pregnancy related complications. Even a moderate amount of weight loss (5 - 10% body weight), before pregnancy, with or without metformin use has shown to be sufficient in improving metabolic markers.^[23]

Metformin used throughout pregnancy in women with PCOS may reduce gestational diabetes incidence by as much

as 9-fold.^[24] Its use during pregnancy in women with PCOS facilitates primary and secondary prevention of gestational diabetes.^[25] The reduction in incidence of gestational diabetes mellitus has been attributed to metformin's metabolic, endocrine, vascular, and anti-inflammatory effects. These effects of metformin were demonstrated in a prospective cohort study wherein 360 non-diabetic PCOS patients participated who conceived while on metformin by different treatment modalities. The study group comprised of 200 women who continued metformin (1000-2000 mg/ day) throughout pregnancy while the control group of 160 women discontinued metformin. The results of the study concluded in favor of the women who continued metformin use who demonstrated statistically significant prevention or reduction in the incidence of gestational diabetes mellitus.^[26]

Of the other studies, which were performed on patients with gestational diabetes, mellitus one was a case controlled study, done on 100 women with GDM who were exclusively treated with metformin, were compared with 100 with GDM-treated exclusively with insulin matched for age, weight, and ethnicity, showed similar baseline maternal risk factors in both groups and similar incidences of gestational hypertension, pre-eclampsia, induction of labor and rate of cesarean section, but significantly greater mean maternal weight gain from enrollment to term in the insulin group. The pregnancy outcomes in the women who were treated with metformin alone, demonstrated lesser incidence of prematurity, neonatal jaundice and admission to neonatal unit with an overall improvement in neonatal morbidity as compared to the women treated with insulin alone. There was no significant difference in the incidence of fetal macrosomia between the 2 groups of women.^[27] Interestingly, a recent randomized controlled trial, done on 100 women with GDM who did not attain euglycemia with diet, were randomized to receive therapy with insulin or oral metformin concluded that metformin was better suited than insulin for prevention of fetal macrosomia, especially in lean or in moderately overweight women developing GDM in late gestation, and insulin was preferred therapy for women with considerable obesity, high fasting blood glucose levels and an early need for pharmacological treatment.^[28]

The beneficial effects of metformin in PCOS women further include weight loss in obese women with significant changes in waist-to-hip ratio, normalization of abnormal LH/FSH ration, and impaired glucose tolerance as well as significant reduction in insulin resistance. Additionally, the use of metformin has a relatively low cost and diminished hazards as compared to those associated with surgical interventions.^[29-31]

A rare but serious side effect reported within 3 weeks of initiation of metformin therapy is a mixed (hepatocellular and cholestatic) type of hepatic damage with raised AST, ALT, ALP and bilirubin levels.^[32-34] However, immediate discontinuation of metformin demonstrated an improvement in symptoms and return of liver enzymes to normal baseline value within 3 weeks. Hence, it is advisable to monitor liver function tests in patients receiving metformin therapy.

CONCLUSION

Metformin (an insulin sensitizing biguanide) is frequently employed for PCOS patients. It has encouraging effects on several metabolic aspects of polycystic ovarian syndrome, such as insulin sensitivity, plasma glucose and lipid profile. Its use in patients with PCOS during pregnancy reduces a number of pregnancy-related complications, such as gestational diabetes and gestational hypertension. Use of metformin throughout pregnancy in women with PCOS has shown to reduce the rates of early pregnancy loss, preterm labor, and prevention of fetal growth restriction. There have been no demonstrable teratogenic effects, intra-uterine deaths, still births or developmental delays reported with metformin use in pregnancy. Despite these favorable effects of metformin use with scarce serious side effects, no definite guidelines recommending metformin use in pregnant women with PCOS exists and hence further research on the topic is necessary.

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