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ORIGINAL ARTICLE

Metformin throughout Pregnancy in Women with Polycystic Ovary Syndrome: Safety and Advantages

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ABSTRACT

Objective: To study the incidence of spontaneous abortions, congenital malformations, neonatal and maternal hypoglycemia after metformin therapy in pregnancy.

Design: Prospective study.

Setting: Outpatient.

Patient(s): 56 women previously oligomenorrheic, nondiabetic women with polycystic ovarian syndrome, who conceived while on metformin.

Intervention(s): Metformin 1 to 1.5 gm/day throughout pregnancy.

Main outcome: Incidence of 1st trimester abortions, gestational diabetes, teratogenicity and maternal complications, like gastritis and hypoglycemia.

Results: On metformin, the incidence of 1st trimester abortion was 11% and the incidence of gestational diabetes was 7%, which is much lower than the incidence otherwise cited for PCOS women. No major congenital abnormalities were observed.

Conclusion: Metformin therapy in pregnancy reduces the otherwise high incidence of 1st trimester abortions, and gestational diabetes in PCOS women is tolerated well and is not found to be teratogenic.

Keywords: Metformin, Polycystic ovary syndrome (PCOS), Pregnancy.

INTRODUCTION

Polycystic ovarian syndrome is characterized by oligomenorrhea and clinical and biochemical hyperandrogenism, and is one of the most common causes of female infertility.[1] Many women with PCOS have hyperinsulinemia secondary to insulin resistance and obesity, and there is a strong evidence to suggest that these elevated insulin levels impede ovulation.[2,3] The insulin sensitizing agent metformin has been shown to ameliorate the endocrinopathy associated with PCOS and facilitates resumption of normal menses in 50 to 90% of these women.[4,5]

As metformin produces regular menstrual cycles and resumption of ovulation in many of the infertile oligomenorrheic women with PCOS, many of these conceive while taking metformin. This raises the question whether metformin should be continued in pregnancy? And if yes, what is the safety of this drug in pregnancy? Metformin is classified as a category B drug by the US Food and Drug Administration. Many studies have shown that metformin therapy when continued in pregnancy reduces the incidence of first trimester abortions and also reduces the development of gestational diabetes, preeclampsia and fetal macrosomia. However, one need to be sure about the safety of this drug in regards to risk of congenital malformations and maternal complications, like hypoglycemia and lactic acidosis before it can be continued in pregnancy to prevent spontaneous abortions and gestational diabetes.

The current study was undertaken to evaluate the safety of metformin in pregnancy. The aim was to study the incidence of congenital malformations and incidence of maternal and fetal hypoglycemia after continuation of metformin in pregnancy. We also simultaneously studied the incidence of spontaneous abortions and gestational diabetes mellitus in these women.

MATERIALS AND METHODS

Revised 2003 ESHRE/ASRM consensus criteria were used to confirm the diagnosis of PCOS (any 2 out of 3): (i) oligomenorrhea or anovulation; (ii) clinical or biochemical signs of hyperandrogenism; (iii) ultrasound picture of polycystic ovaries; and exclusion of other diseases, like hypothyroidism,

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hyperprolactinemia and congenital adrenal hyperplasia. Exclusion criteria included serum creatinine > 1.5 gm/day, pituitary insufficiency and known case of diabetes.[6]

Study Patients

Ninety-eight nonpregnant women with PCOS with complaint of infertility attended our infertility clinic between years 2003 and 2004. All these women were started on metformin 1 to 1.5 gm/day. Of these, 56 subsequently conceived (16 naturally while on metformin, 28 after IUI and another 12 after IVF/ICSI). These 56 women were then enrolled for the present study and followed up till delivery. Metformin was continued throughout pregnancy at the preconceptional dose.

During pregnancy, all women underwent regular antenatal follow-up. A check was kept on hemoglobin and blood pressure. Prenatal screening with triple marker was done for all women. Also, a 3D sonography was done at 16 to 18 weeks to detect fetal anomalies. Serial sonographies were done to assess the fetal well-being. All patients underwent screening test for gestational diabetes at 24 to 28 weeks. Obstetric charts were maintained for these women and they were followed till delivery. The incidence of spontaneous abortions, multiple pregnancies, gestational diabetes, pregnancy induced hypertension, congenital defects, fetal and maternal hypoglycemia were noted.

RESULTS

Baseline Characteristics of the Women before Metformin Therapy

All 56 women met the revised 2003 ESHRE/ ASRM consensus criteria for diagnosis of PCOS. Out of these, 40 women were oligomenorrheic and 16 were amennorheic. Clinical hyperandrogenism was present in 28 (50%) women and biochemical hyperandrogenism in 40 women. Of the 56 women, 55 were diagnosed to have PCO pattern on pelvic ultrasound.

The mean and median age of the women at the time of conception were 28.3 ± 3.6 and 28 years. About 40 women were between 20 and 30 years and 16 were between 30 and 40 years. The median BMI for the cohort was 30.7 kg/m^2 which falls in the obese category. Body mass index (BMI) was normal in 24/56 (42.8%) women, overweight in 16/56 (28.5%) women and obese in 16/56 (28.5%) women.

All but three women had primary infertility. These three women had history of recurrent spontaneous abortions (two women had two prior abortions and third one had three prior abortions), followed by secondary infertility.

MODE OF CONCEPTION

Table 1 shows the various modes of conception in the 56 women while on metformin therapy.

Antenatal Events

Spontaneous Abortion

First trimester abortion occurred in seven out of 56 women (11%). Of these, one woman was with twin gestation, rest all were singleton pregnancies. Out of three women with history of recurrent abortions, only one had miscarried at 8 weeks; the other two had successful pregnancies and delivered healthy baby at term.

Multiple Pregnancies

The incidence of multiple pregnancies (all twins) was 12.5% (8 out of 56). Six of these women had multiple gestations following IVF/ICSI. One woman had twins following artificial insemination while another woman had spontaneous twin gestation while on metformin therapy.

Gestational Diabetes

Four women developed gestational diabetes diagnosed by glucose challenge test at 24 weeks. Only one of these four women required insulin therapy to control blood sugar, rest were controlled by diabetic diet.

Macrosomia

The average newborn weight was 2.62 kg. None of the neonate was observed to have macrosomia.

Congenital Malformations

Only one baby was diagnosed to have tracheoesophageal fistula. This was repaired surgically and a follow-up at 3 and 6 months showed no complications.

Maternal Complications

The most frequent complaint among the mothers was gastritis which was relieved with antacids. There was no incidence of maternal hypoglycemia or lactic acidosis.

Table 2 below summarizes the various antenatal events.

Table 1: Various modes of conception in women on metformin therapy

Metformin +	*No. of women*
Natural	16
OI + IUI	28
IVF/ICSI	12

Table 2: Summary of various antenatal events with patients on metformin

Obstetric events	*No. of women (n = 56)*
Spontaneous abortion	7 (11%)
Gestational diabetes	4 (7%)
PIH	8 (14%)
Preterm labor	5 (9%)
Congenital anomalies	1(tracheoesophageal fistula)
Macrosomia	Nil
Maternal complications	
Gastritis	14
Hypoglycemia	Nil
Lactic acidosis	Nil

DISCUSSION

Polycystic ovarian syndrome is the most common causes of anovulation and female infertility. Not only these women are infertile but also more likely to have pregnancy complications, like spontaneous abortions and gestational diabetes, compared to the general population. Recent understanding of polycystic ovarian syndrome has revolutionized the treatment options available for these women. Metformin, an insulin sensitizing agent, is known to restore regular ovulatory menstrual cycle in majority of these oligomenorrheic PCOS women many of whom thereafter conceive naturally.[4] Besides helping in conception, it is also shown to improve the pregnancy outcomes in these women by reducing the incidence of spontaneous abortions, gestational diabetes and macrosomia.

Various studies have shown that women with PCOS have increased chances of abortion in the first trimester.[7,8] The various reasons cited for this increased occurrence abortions are increased LH levels, hyperandrogenism, hyperinsulinemia and increased PAI-I activity. High PAI-I activity is known to cause thrombosis in the placental circulation thereby causing placental insufficiency.[9,10] Various other studies have reported that metformin decreases the incidence of spontaneous abortions in women with PCOS.[11,12] The exact mechanism by which metformin prevents abortions is not known but many possibilities are suggested: Decreasing androgen, decreasing insulin levels, decreasing PAI-I activity[13] or by improving oocytes quality. In a recent study conducted by Zolghadri et al, it was found that the abortion rate was significantly reduced after metformin therapy in women with history of recurrent abortions in comparison to the placebo group (15% *vs* 55%).[14] In the index study, the incidence of spontaneous abortion among these PCOS women was 11% much lower than that cited otherwise in PCOS women. Also, of the three women with BOH and previous recurrent abortions, only one aborted, the other two carried pregnancies till term and had a successful outcome.

Women with PCOS are at increased risk of gestational diabetes and type II diabetes mellitus later in life.[15,16] Obesity, advanced age at conception and preconception insulin resistance predispose these women to gestational diabetes. In a study by Lo et al, women with PCOS were observed to have a 2.4 fold increased risk of gestational diabetes which was independent of age, race, ethnicity and multiple gestations.[16] It has been shown that the incidence of gestational diabetes in women with PCOS does not differ from normal pregnant controls, if these women are given metformin throughout pregnancy.[17,18] In a case control study conducted by Nawaz et al, it was observed that continuous use of metformin during pregnancy significantly reduces the rate of miscarriage, gestational diabetes requiring insulin treatment and fetal growth restriction. No congenital anomaly, intrauterine death or stillbirth was reported in this study.[19] In the index study, the incidence of gestational diabetes was 7%, much lower than otherwise cited in women with PCOS without metformin.

Metformin has not shown to be teratogenic when given during pregnancy.[19,20] In the current study also there was no increase in the incidence of birth defects and only one neonate was found to have tracheoesophageal fistula. Also a study by Glueck et al has shown that continuing metformin in pregnancy does not affects the birth length or weight, growth or motor or social development of these children in the first 18 months of life.[21]

Thus, from this study, we speculate that metformin not only helps women with PCOS conceive but also promotes prevention of spontaneous abortion and development of gestational diabetes in women with PCOS. Moreover, it is not shown to be teratogenic and does not affect the neonatal development. However, the study was limited by the lack of randomized double blind PCOS group on placebo therapy.

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