

Effect of Metformin on Miscarriage in Pregnant Patients with Polycystic Ovary Syndrome

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ABSTRACT

Background: This study was performed with the aim of evaluating the effect of metformin in reducing miscarriage when continued until the end of the first trimester of pregnancy in patients with polycystic ovary syndrome (PCOS) and infertility.

Subjects and Method: From January 2004 to December 2005, a total of 75 pregnant women with PCOS were studied 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. The results of this study were then assessed using chi-square McNemar's, ANOVA Kruskal Wallis and logistic regression tests.

Results: There was 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. Fetal anomalies were absent in all three groups.

Conclusion: According to the current findings, it seems that continuing metformin during the first trimester of pregnancy has beneficial effects in patients with PCOS.

Efecto de la Metmorfina Sobre los Abortos Espontáneos de Pacientes Embarazadas que Presentan el Síndrome de Ovario Poliúístico

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RESUMEN

Antecedentes: Este estudio fue realizado con el propósito de evaluar el efecto de la metmorfina en la reducción de abortos espontáneos cuando se la continúa hasta el final del primer trimestre de embarazo, en pacientes con síndrome de ovario poliúístico (SOPQ) e infertilidad.

Sujetos y Método: De enero 2004 a diciembre 2005, fueron estudiadas en tres grupos diferentes, un total de 75 mujeres embarazadas que presentaban SOPQ. En el grupo A, la administración de metmorfina (TDS) 500 mg tres veces al día se detuvo inmediatamente después del diagnóstico del embarazo (5 – 6 semanas de gestación); en el grupo B, se administró la metmorfina hasta el final de las 8 semanas de gestación, y en el grupo C hasta el final de las 12 semanas de gestación. Los resultados de esta estudio fueron entonces evaluados usando chi-cuadrado McNemar's, ANOVA Kruskal Wallis y teste de regresión logística.

Resultados: Hubo una diferencia estadística significativa entre los abortos espontáneos previos y los corrientes en los embarazos corrientes, con una disminución del 40% al 8% en el grupo B, y del 32% al 4% en el Grupo C. A pesar de la reducción de la tasa de abortos espontáneos observada en el grupo A, del 20% al 4%, la diferencia no fue estadísticamente significativa. Las anomalías fetales estuvieron ausentes en los tres grupos.

Conclusión: De acuerdo con los hallazgos actuales, parece que la continuación de la metformina durante el primer trimestre del embarazo, tiene efectos beneficiosos en los pacientes con SOPQ.

West Indian Med J 2009; 58 (5): 434

INTRODUCTION

Polycystic ovary syndrome (PCOS) is found in 4–6% of women in the reproductive age (1). Its common clinical manifestations are insulin resistance, hyperandrogenism, anovulation and consequently, infertility. Affected women are also at higher risk of developing diabetes mellitus, atherosclerosis and cardiovascular disease. The use of insulin-sensitizing drugs like metformin results in a decrease in LH and androgen levels with a return of regular menstrual cycles and ovulation (1, 2). Metformin can significantly affect women of the reproductive age with PCOS, especially those who are resistant to ovulation-inducing drugs such as clomiphene (2). In addition to the higher prevalence of infertility among women with PCOS, there is also a higher risk of miscarriage due to hyperandrogenism, high LH level and higher insulin resistance among those who do become pregnant (3, 4). Considering the significant therapeutic effects of metformin in decreasing insulin and androgen levels in these subjects, it seems that the administration and maintenance of metformin until the end of the first trimester of pregnancy (end of 12 weeks gestation) can considerably decrease the rate of miscarriage and thus improve the quality and outcome of pregnancy (2, 4). For a long period of time, the use of metformin and other oral antidiabetic drugs during pregnancy were contraindicated (5). Recently, some studies on animal models and clinical trials on humans have shown that the use of metformin during pregnancy does not increase the risk of fetal or maternal complications or anomalies. In other words, metformin is perhaps the only known non-teratogenic oral antihyperglycaemic drug available (6–9) although there are not yet results of double blinded placebo controlled studies which would assess the pregnancy outcomes and absolute safety of metformin. This study was performed with the aim of determining the effect of maintaining metformin use until the end of 8 and up to 12 weeks of gestation on miscarriage rate and to compare it with its cessation immediately after diagnosis of pregnancy.

SUBJECTS AND METHODS

This clinical trial was performed as a research project from January 2004 to December 2005 after obtaining approval from the Ethics Committee of Tehran University of Medical Sciences.

In this trial, a total of 75 women with a history of infertility due to PCOS, who had become pregnant with clomiphene citrate (generic Iranian Brand) administered 50 or 100 mg daily for 5 to 7 days and metformin (Gluco-phage®, Merck Sante France) administered 1500 mg daily, were enrolled after agreeing to participate in the study. The subjects were interviewed by trained midwives in three

separate clinics and information including obstetrical history, history of infertility, method of stimulation of ovulation, pregnancy-associated complications as well as variables including body mass index (BMI) were noted in the mother's questionnaire form. In the next stage, after obtaining written consent, the subjects were studied in three therapeutic groups: Group A discontinued metformin immediately after diagnosis of pregnancy between 5–6 weeks gestation ($n = 25$), Group B maintained the use of metformin until 8 weeks gestation ($n = 25$) and Group C until 12 weeks gestation ($n = 25$). The subjects were then followed throughout pregnancy for probable complications and outcome of pregnancy. Inclusion criteria included pregnant women with a history of infertility which was solely due to PCOS (based on the Rotterdam Criteria (10) and confirmed by the physician) and who received metformin along with other ovulation-inducing drugs prior to pregnancy. Exclusion criteria included reluctance to take the drugs during pregnancy. Data were processed using SPSS (version 15). Analytical tests showed significant 95% relationship using chi-square, McNemar's, ANOVA, Student's *t-test*, Kruskal Wallis and logistic regression tests.

RESULTS

In the 75 pregnant women studied, 71 cases of full-term deliveries and four cases of miscarriage were seen in all three groups. Table 1 shows the distribution of demographic characteristics of the subjects. As shown, there was no significant difference between the three groups according to background features. History of previous miscarriage was compared with that of present pregnancies, independently, inside each group as well as between the groups. In Group B, eight women had a history of miscarriage in their previous pregnancies, with only one miscarriage while using metformin in current pregnancy, which shows a significant fall from 32% to 4% ($p < 0.008$). In Group C, there were 10 cases of prior miscarriage which was reduced to two with the use of metformin, which also indicated a significant reduction from 40% to 8% ($p = 0.002$). In group A, six mothers had a history of previous miscarriage while only one miscarriage was reported in the study group with a fall from 20% to 4%. According to McNemar's test, this difference was not statistically significant ($p = 0.125$). McNemar's test also failed to show any significant statistical relationship between the three groups with respect to history of previous and current rate of miscarriage. It is worthy of mention that, in all the groups, the miscarriages which did occur were in the same women who previously had an early pregnancy loss. Regarding BMI in the three groups, student's *t-test* and regression tests did not show a significant statistical

Table 1: Frequency distribution of quantitative variables among the groups under study prior to therapy

Quantitative Variables Number	Age (years)**	Duration of infertility (years)*	Number of previous deliveries*	Number of previous abortions*	BMI*
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Group A (before 8 weeks) n = 25	27.96 ± 5.70	3.53 ± 2.52	1.50 ± 0.70	0.30 ± 0.61	24.5 ± 3.17
Group B (8 weeks) n = 25	28.72 ± 3.57	2.55 ± 1.54	1.64 ± 0.81	0.44 ± 0.71	25.19 ± 16.39
Group C (12 weeks) n = 25	26.80 ± 3.88	4.07 ± 2.46	1.52 ± 0.65	0.48 ± 0.65	27.55 ± 5.17
Total n = 75	27.82	3.38 ± 2.19	1.55 ± 0.71	0.40 ± 0.65	25.7 ± 5.28
p Value	0.115	0.75	0.81	0.47	0.51

*Kruskal Wallis Test

**ANOVA test

Table 2: Frequency distribution of miscarriage among the groups under study prior to and after therapy.

Study Groups	Previous miscarriage No (%)	Current Miscarriage No (%)	p value
	Group A	6 (20%)	
Group B	8 (32%)	1 (4%)	0.008
Group C	10 (40%)	2 (8%)	0.002

McNemar's test

relationship between mean BMI with occurrence of current or previous miscarriage.

DISCUSSION

Polycystic ovary syndrome is one of the most common endocrine disorders among women of the reproductive age and is seen to affect about 4%–6% of all women (1). The use of insulin-sensitizing drugs such as metformin leads to a reduction in the level of insulin and thus a reduction in LH and androgen levels thereby regulating the menstrual cycle and ovulation. Different studies show that the rate of miscarriage is higher if pregnancy occurs in patients with PCOS, and the use of metformin can reduce this rate (2, 3, 11, 12). The current study, which was conducted on three therapeutic groups showed that the rate of miscarriage was significantly lower in the groups using metformin until 8 weeks gestation (Group B) and 12 weeks gestation (Group C) *ie* 4% and 8% respec-

tively. This miscarriage rate is lower or similar to the rate of fetal loss in the total population (13, 14).

In a study by Glueck *et al*, the miscarriage rate in 100 patients with PCOS retrospectively was 62% and reduced to 17% while receiving metformin during pregnancy (2). According to Glueck, reduction in the rate of abortion is due to plasminogen activator inhibitors which results in improved nesting (8). Also, according to Jakubowicz, metformin can enhance uterine blood flow (3). Thatcher *et al* have considered a better quality of egg cell due to induction ovulation to be the reason for the reduced miscarriage rate (9). According to the current study, it seems that maintenance of metformin until 12 weeks gestation can be more effective in reducing miscarriage rate. In the current study, mean BMI was equal in all three groups. According to some studies there is a relationship between high BMI and higher fetal loss rate (11). Nevertheless, a significant statistical relationship was not observed between BMI and miscarriage rate in this study. Therefore, it seems that metformin is capable of decreasing the rate of fetal loss by a mechanism other than its effect on maternal body weight.

Inadvertent use of metformin during pregnancy by patients with gestational diabetes, although being considered as a teratogenic drug for many years, has been cleared as safe by the Food and Drug Administration (FDA).

Today, studies show that the maintenance of metformin use during the first trimester of pregnancy is not associated with any fetal anomalies. Review articles by Koren *et al* in five separate cohort studies in 2006 showed that the rate of

congenital anomalies does not increase with metformin (12). In the present study, there were no neonatal anomalies. Experimental studies performed on animal models show that a relative transplacental passage of metformin does take place. Charles *et al* showed that its transplacental passage may result in complications such as obesity and iatrogenic insulin resistance in the newborn (15, 16). Therefore, more widespread studies must be performed in this field in order to confirm its safety.

In summary, considering the findings of this study as well as those of previous ones, it seems that maintenance of metformin use during pregnancy may reduce miscarriage rate as well as improve the process of pregnancy. However, in order to confirm the safety and advantages of metformin use during pregnancy, more widespread studies on a larger number of patients with PCOS will be required.

ACKNOWLEDGEMENTS

This research was approved and supported by the Dean of research of Tehran University of Medical Sciences and Health Services under grant number 132.9074, Dec 2003 for which we would like to express our gratitude. We would also like to thank our colleagues at the Vali-e-Asr Reproductive Health Research Center and the Infertility Clinic of Vali-e-Asr Hospital for their cooperation.

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