Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 266–269

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome

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ARTICLE INFO

Article history:
Accepted 19 June 2013

Keywords:
early pregnancy loss
insulin resistance
metformin
polycystic ovary syndrome

ABSTRACT

Objective: To evaluate the effectiveness of metformin therapy in reducing early pregnancy loss in pregnant women with polycystic ovary syndrome (PCOS).
Materials and methods: This is a prospective cohort study conducted in the Obstetric Department of the Gulf Medical College Hospital in Ajman, UAE, for a period of 3 years. This study involved 106 nondiabetic pregnant women with PCOS who became pregnant while using metformin. They were divided into two groups, namely, the group that received metformin throughout pregnancy (metformin group) and the group that discontinued using the drug once pregnancy started (control group). A comparison was made between the two groups of patients with respect to certain basal characteristics (age, body mass index, previous obstetric outcome, serum glucose with free testosterone). Statistical analysis was performed using Chi-square test to compare the differences between the two groups.
Results: There were 56 patients who received metformin during pregnancy (metformin group) compared with 50 patients who did not receive the treatment (control group). The rate of early pregnancy loss in the metformin group was 8.9% (5/56) compared with 36% (18/50) in the control group ($p < 0.001$). For patients in the metformin group with a history of previous miscarriage, the rate of pregnancy loss was 45% (35 cases/50 pregnancies).
Conclusion: Metformin therapy in pregnant women with PCOS was associated with a significant reduction in the rate of early pregnancy loss.

Introduction

Although the first description of polycystic ovary syndrome (PCOS) is generally credited to Stein and Leventhal (1935), it may have been observed as early as 1721 when Italian scientist Antonio Vallinsneri observed larger-than-normal ovaries in young peasant women, who were moderately obese and infertile [1].

PCOS is the most common cause of anovulatory infertility worldwide. In addition to poor conception rate, early pregnancy loss rates are significantly higher (30–60%) than in the general population [2,3]. The etiology of this condition is unknown. Hyperinsulinemic resistance is implicated as an independent risk factor for early pregnancy loss due to its adverse effects on endometrial function and implantation environment. Hyperinsulinemic resistance also plays a key role in the disorder by increasing androgen concentration and impending ovulation [4,5].

Administration of various insulin-sensitizing drugs such as metformin has been shown to reduce androgen concentration with restoration of ovarian cycles and reduction of early pregnancy loss [6].

The beneficial effects of metformin have been reported in previous studies [7–9] but the question arises whether its use can be continued throughout pregnancy.

Metformin pharmacology

Metformin, a biguanide, is an antihyperglycemic drug, which improves glucose tolerance. It lowers the basal and postprandial plasma glucose concentrations. Metformin decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity by increasing glucose uptake and utilization [6].

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http://dx.doi.org/10.1016/j.tjog.2013.06.020

In patients with PCOS, metformin reduces fasting insulin, stimulating luteinizing hormone (LH), and free testosterone levels [10]. During pregnancy, the drug passes through the placenta to the fetus and the fetal serum level becomes comparable to the maternal level but it is generally considered a safe treatment during pregnancy [11]. The United States Food and Drug Administration has classified the drug as a category B medication, suggesting that it does not appear to cause harm to the fetus in animal studies [12–14].

It is documented that metformin has beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to early pregnancy loss [15]. However, its use to reduce pregnancy complications in women with PCOS is still controversial [16].

This study was undertaken to evaluate the effect of metformin therapy on pregnancy outcome by comparing the rate of early pregnancy loss between two groups of patients who received or did not receive it throughout the pregnancy period.

Materials and methods

This is a prospective cohort study conducted in the Obstetric Department of the Gulf Medical Hospital in Ajman between January 2008 and January 2011.

Participants in the study were 106 nondiabetic pregnant women who conceived while taking metformin. The patients were divided into two groups: The first group who became pregnant while receiving metformin and continued the treatment at a dose of 1000 mg/d (metformin group; $n = 56$) and the second group who discontinued the use of the drug once pregnancy started because they were unwilling to continue its use (control group; $n = 50$).

The study protocol has been revised by the Ethical Committee of Gulf Medical University, and verbal consent was obtained from the patients. The complete history of the study patients and their clinical examination results were completely reviewed to determine their age, previous history of miscarriage, and body mass index (BMI).

Specific investigations of serum analysis were carried out for LH, thyroid function test, free testosterone level, and oral glucose tolerance test.

The inclusion criteria of the study were the diagnosis of PCOS before pregnancy, maternal age of 18–40 years, gestational age between 5 weeks and 12 weeks, normal serum thyroid-stimulating hormone and prolactin levels, and pregnancy with singleton fetus.

The exclusion criteria were other risk factors for miscarriage such as abnormal serum karyotyping for both parents; antiphospholipid syndrome, which was excluded by anticoagulant antibodies test; uterine anomalies as excluded by transvaginal ultrasound scanning; and diabetes mellitus by oral glucose tolerance test.

The diagnosis of PCOS was based on the Rotterdam criteria [17] implying that at least two of the following three criteria were fulfilled: presence of polycystic ovaries ($\geq$ 9 subcapsular follicles of 10 mm by transvaginal ultrasonography), oligomenorrhea (length of menstrual cycles > 35 days or < 10 menstrual cycles/y), anovulation, and serum-free testosterone level > 2.5 nmol or clinical signs of hirsutism.

Pregnancy was detected by serum beta-human chorionic gonadotropin level > 50 IU/L [18] with confirmation of intrauterine pregnancy by transvaginal ultrasound scanning. Early pregnancy loss was defined as spontaneous loss before 12 completed weeks of pregnancy [19], and was documented as the absence of fetal viability that was confirmed by the ultrasonography.

For statistical analysis, Chi-square test was used to compare the differences in the rates of early pregnancy loss between the two groups and two-tailed test was used for independent samples. Results were reported as means ± standard deviation and $p < 0.05$ was considered significant.

Results

Table 1 demonstrates the basal clinical and biochemical characteristics of patients in the metformin and control groups. There were no significant differences with respect to maternal age, BMI, fasting glucose concentration, and serum-free testosterone level between the metformin and control groups (Table 1).

In the metformin group, nine patients met all the five criteria of PCOS described in the *Materials and methods* section. A total of 15 patients and 20 patients, respectively, met two and three criteria; 12 patients met four of these criteria. In this group, the mean gestational age was 8.6 ± 0.2 weeks and 50% of the patients (28/56) became pregnant with the use of clomiphene citrates or human chorionic gonadotropin for induction of ovulation. Four patients (7.1%) conceived after *in vitro* fertilization procedure. None of the women in the two groups had diabetes mellitus before conception and all had normal blood glucose level at a range of 5.6 ± 0.6 mmol/L in the metformin group and 5.2 ± 0.4 mmol/L in the control group.

The rate of early pregnancy loss with the results of previous pregnancy outcome is described in Table 2. Among the 56 women who received metformin throughout the pregnancy period, there were five cases (8.9%) of early pregnancy loss, whereas there were 18 cases (36%) in the control group. The difference was significant ($p < 0.001$; Table 2).

The results of the previous pregnancy outcome in the patients studied showed that among the 56 women in the metformin group, there were 25 cases with a positive history of early pregnancy loss in previous pregnancies and 31 had a negative history. Patients with a negative history of early pregnancy loss were either primigravidas or cases with previous successful pregnancies. None of the patients had received metformin in the previous pregnancies.

Among the 25 women in the metformin group with a history of previous pregnancies, there were 50 pregnancies (15 live births and 35 miscarriages), with a miscarriage rate of 45%.

In the control group, 20 (40%) of the 50 women had a history of previous pregnancy loss, whereas 30 cases were primigravidas. Among the 20 women with previous pregnancy loss, there were 25 pregnancies, which resulted in 16 live births and nine miscarriages, yielding a miscarriage rate of 36%. For the patients in the metformin group with a previous history of early pregnancy loss, there was a reduction in the rate of pregnancy loss from 45% in the previous pregnancies to 8.9% in the present pregnancies. In the control group, however, there were no significant differences between the rates in the previous and present pregnancies (40% vs. 35%), respectively.

The analysis of the effect of metformin on the maternal androgen and BMI shows that there was a significant reduction in the level of free testosterone in the serum of patients in the metformin group compared with those in the control group (1.6 ± 0.5 nmol/L vs. 4.2 ± 0.7 nmol/L). However there were no significant differences of BMI in the two groups. In addition, it was observed that most cases of pregnancy loss in the metformin and control groups were associated with elevated serum-free testosterone level (> 4 nmol/L) and higher BMI (> 29 kg/m^2; Table 3).

Metformin was well tolerated in all patients. None of the patients required cessation or reduction in the treatment dose. No side effects or serious complications were observed.

Discussion

Women with insulin resistance are at increased risk of hyperinsulinemia, PCOS, and hyperandrogenism [4,5]. They are also at