Objective: To determine the incidence of an abnormal glucose tolerance test in patients with recurrent spontaneous abortion and whether metformin would safely reduce the rate of first trimester spontaneous abortions in patients without polycystic ovary syndrome (PCOS) as well as with PCOS and an abnormal glucose tolerance test.

Design: Prospective control clinical trial.

Setting: Shiraz University-affiliated hospital.

Patient(s): Patients with a history of recurrent spontaneous abortion and women with a history of normal full term pregnancy.

Intervention(s): The incidence of abnormal carbohydrate metabolism was determined. Metformin and placebo were given to women with an abnormal glucose tolerance test and who had recurrent spontaneous abortions.

Main Outcome Measure(s): Continuation of pregnancy beyond the first trimester in all groups and presence or absence of teratogenicity in the delivered baby after metformin therapy.

Result(s): Twenty-nine of the patients in the group with recurrent spontaneous abortion were found to have an abnormal glucose tolerance test result compared with just four (5.4%) patients in the normal pregnancy group. The abortion rate was significantly reduced after metformin therapy in patients without PCOS in comparison to the placebo group (15% vs. 55%).

Conclusion(s): This study indicates an important link between an abnormal glucose tolerance test and a history of recurrent abortion. It was also found that metformin therapy improves the chances of a successful pregnancy in patients with an abnormal glucose tolerance test. (Fertil Steril 2008;90:727–30. ©2008 by American Society for Reproductive Medicine.)

Key Words: Recurrent abortion, abnormal glucose tolerance test, metformin

Recurrent spontaneous abortion is defined as the loss of three or more consecutive pregnancies before the 20th week of gestation or a fetal weight of less than 500 g (1–3). Many causes of recurrent abortions have been identified including chromosomal abnormality, congenital or acquired uterine malformation, incompetent cervix, inadequate luteal phase, certain infections and immunologic diseases (4–7). The relationship between recurrent spontaneous abortion and abnormal glucose tolerance has not been thoroughly identified.

Some investigators believed that diabetes mellitus or an abnormal glucose tolerance test (GTT) could be implicated as a cause for recurrent abortion (1, 6, 8, 9), whereas others claimed that there was actually very little evidence to support the association between diabetes and abortion (4, 5). For those women with polycystic ovary syndrome (PCOS), conception rates are poor and pregnancy loss during the first trimester is high (30%–50%). The latter problem could be attributed to insulin resistance or hyperinsulinemia (10–12).

Some research suggests that metformin improves glucose intolerance in patients with PCOS (13–16) and confirm that if metformin therapy is continued during the pregnancy it could improve the outcome (14, 15, 17). Metformin is not teratogenic and is classified as a class B drug by the Food and Drug Administration in the United States (14, 15). There have been previous studies showing the positive effects of metformin in patients with PCOS and recurrent abortions. This is the first study that is chiefly concerned with determining the incidence of abnormal GTT among patients with unexplained recurrent abortion and to investigate the positive effects of metformin in reducing the abortion rate in patients without PCOS but with an abnormal GTT.

METHODS AND MATERIALS

Patients

This study was carried out at Shiraz University-affiliated hospital. All tests and procedures in this study were approved by the Shiraz University institutional review board (IRB). All
patients gave signed informed consent. Patients who had unexplained recurrent abortions were defined as having three or more repeated consecutive abortions with normal karyotype, hormonal assay (thyroid function test and PRL), hysterosalpingogram or hysteroscopy, anticardiolipin antibodies, lupus anticoagulant, PT, and PTT.

An impaired GTT was diagnosed with the presence of blood sugar between 140 and 200 mg/dL 2 hours after the ingestion of 75 g of glucose and the diagnosis of PCOS was made on the basis of chronic oligomenorrhea (defined ≤6 menses per year), clinical and biochemical hyperandrogenism (hirsutism, severe acne, and high levels of total or free T, androstenedione [A], and DHEAS), and exclusion of the hypothyroidism, hyperprolactinemia, and congenital adrenal hyperplasia. Ancillary diagnostic criteria for PCOS were presence of >10 follicles of 2–10 mm in diameter and increased density of ovarian stroma in transvaginal sonography (Adam S et al 1985).

Study Protocol
This study was done in two steps between August 2003 and June 2005.

Step One
In step one we compared two groups of patients. The first group comprised 164 women with a history of recurrent spontaneous abortion and in the second group there were 74 women who had previously experience at least two normal full term pregnancies. The patients in both groups were aged between 18 and 39 years and they all underwent a GTT.

Step Two
Of the group of patients with recurrent spontaneous abortion and impaired GTT, only 29 were enrolled in this step of the study. These patients were evaluated for the diagnosis of PCOS and non-PCOS symptoms and then they were divided into four groups according to a computer randomization method and medication were given in a double blind method.

- Group I: Patients with PCOS on metformin therapy (4 patients)
- Group II: Patients with PCOS on placebo therapy (3 patients)
- Group III: Patients without PCOS on metformin therapy (13 patients)
- Group IV: Patients without PCOS on placebo therapy (9 patients)

We started metformin (1,500 mg/day) and placebo before conception and we repeated the GTT every month in the patients receiving metformin and if the GTT was normal we allowed the patient to get pregnant. Metformin therapy continued. All groups had monthly follow-up visits throughout the pregnancy and were managed according to a high risk pregnancy protocol (15).

Outcome Measures
Outcome measures included normal ongoing pregnancies ≥14 weeks in the four groups and absence or presence of anomaly in the baby after delivery.

Statistical Analysis
Fisher’s exact test was carried out to determine GTT results in all patients and for comparison of abortion rates in patients with and without PCOS on metformin or placebo therapy.

RESULTS
All patients were aged between 18 and 39 years. In the recurrent spontaneous abortion group, the mean age was 26.4 years (±SD) and in the normal pregnancy group, the mean age was 25.9 years (±SD). The number of previous abortions in the recurrent spontaneous abortion group ranged from 2–7. Of the 164 patients with a history of recurrent spontaneous abortion, 29 patients (17.6%) had an abnormal GTT and 2 patients had a GTT result of more than 200 mg/dL. These two patients were then excluded from the study due to the diagnosis of overt diabetes mellitus.

Of 74 women in the abnormal GTT and 2 patients had a normal group with previous norma births, 4 (5.4%) women had an abnormal GTT and 0 (0% had a normal GTT. In the patient group and the normal group the difference of abnormal GTT was statistically significant (odds ratio [OR] 1.34, 95% confidence interval [CI] 0.25–2.42, \( P = 0.017 \)) (Table 1).

In step two of the study, the four patient groups had an age range of 18–39 years. In placebo group the mean age was 25.1 years (±SD) and in the metformin group it was 25.4 years (±SD).

The four groups are compared in terms abortion rate between placebo and metformin therapy in patients with and without PCOS in Table 2. The abortion rate was significantly decreased after metformin therapy in the patients without PCOS compared to the placebo group (15% vs. 55%; OR 2.4, 95% CI 0.35–4.4, \( P = 0.02 \)) and although the abortion rate decreased after metformin therapy in the patients with

<table>
<thead>
<tr>
<th>The difference in rates of abnormal glucose tolerance test (GTT) between patient group and normal group.</th>
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</thead>
<tbody>
<tr>
<td>Normal GTT</td>
</tr>
<tr>
<td>Patient group</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>( P ) value</td>
</tr>
</tbody>
</table>

TABLE 2

Abortion rate in the four study groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Aborted</th>
<th>Abortion rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>4</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>GII</td>
<td>3</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>GIII</td>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>GIV</td>
<td>9</td>
<td>6</td>
<td>55</td>
</tr>
</tbody>
</table>


PCOS, the P value was not statistically significant (25% vs. 66%; P=.42).

DISCUSSION

Sutherland and Fisher (9) found in their study an association between inadequately explained stillbirth and recurrent abortion and abnormal glucose tolerance.

Another report by Kaban and Baird showed higher rates of fetal loss in diabetic mothers in comparison to normal healthy women (15). On the other hand Crane and Wahl (4) studied the incidence of spontaneous abortion among 154 diabetic women and showed similar abortion rates in diabetic and normal healthy women concluding that routine GTT was not a sufficient indicator in the evaluation of patients with habitual abortions. However, our study showed that the incidence of an abnormal GTT is more evident in women with recurrent abortions compared to women who had normal full term pregnancies (17.9% vs. 5.4%). Notably, these results are comparable with the findings in the studies by Sutherland and Dekabor.

Many studies confirmed that women with PCOS and an abnormal GTT had a higher risk of early abortions (11, 13–15). Previously, it was demonstrated that the administration of metformin to pregnant women with PCOS and an abnormal GTT leads to a significant reduction in the rate of early pregnancy loss (11, 13–15). We also found that PCOS and abortion rates decrease significantly with metformin therapy in patients who have an abnormal GTT with or without PCOS.

Although in previous studies the effect of metformin was shown only in patients with PCOS and an abnormal GTT and recurrent abortion, we also showed the beneficial effects of metformin on patients with abnormal GTT and the non-PCOS status (P=.03). Although the abortion rate decreased in patients with PCOS the P value was not found to be significant (P=.49).

The findings of the present study support the hypothesis that the decrease in insulin resistance and the normalizing effect on GTT with metformin dramatically decreases the rate of early pregnancy loss. Metformin administration may have decreased the rate of early pregnancy loss by several mechanisms. One of the effects may be its action to improve insulin sensitivity in patients with an abnormal GTT. A study implicated insulin resistance as an independent risk factor for early pregnancy loss in women with PCOS. The investigators showed that hyperinsulinemia adversely affected endometrial function and the preimplantation environment by decreasing glycodelin and insulin-like growth factor (IGF)-binding protein 1 (9, 15, 18). Glycodelin may play a role in inhibiting the endometrial immune response to the embryo (14, 15). This mechanism may also be an explanation for the decreased abortion rate after metformin therapy in patients with abnormal GTT with or without PCOS. In addition, it has been stated that plasma plasminogen activator inhibitor 1 concentrations are increased in the insulin resistance state, including PCOS (14, 19–21).

Increased plasminogen activator inhibitor 1 concentration is an independent risk factor for miscarriage in PCOS, presumably by inducing a hypofibrinolytic state (19–22). Metformin administration has been reported to decrease circulating plasminogen activator inhibitor 1 in women with PCOS (14) and it could be a possible mechanism in all the patients with abnormal GTT including women without PCOS. Metformin is classified as a category B drug, indicating that no teratogenic effects have been demonstrated in animal studies (13).

In conclusion, the present study showed a relationship between abnormal GTT and recurrent abortion as well as the effect of metformin in improving the outcome of pregnancy in patients with or without PCOS who also have an abnormal GTT. Therefore we recommend performing GTT screening for all patients at risk of recurrent abortions and to consider the positive value of metformin therapy in the treatment of patients with abnormal GTT, regardless of the presence of PCOS symptoms.

REFERENCES


