Effects of Metformin on Early Pregnancy Loss in the Polycystic Ovary Syndrome

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Polycystic ovary syndrome is the most common form of female infertility in the United States. In addition to poor conception rates, pregnancy loss rates are high (30–50%) during the first trimester. We hypothesized that hyperinsulinemic insulin resistance contributes to early pregnancy loss in the syndrome, and that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy would reduce the rate of early pregnancy loss.

We conducted a retrospective study of all women with polycystic ovary syndrome who were seen in an academic endocrinology clinic within the past 4.5 yr and who became pregnant during that time.

Sixty-five women received metformin during pregnancy (metformin group) and 31 women did not (control group). The early pregnancy loss rate in the metformin group was 8.8% (6 of 68 pregnancies), as compared with 41.9% (13 of 31 pregnancies) in the control group ($P < 0.001$). In the subset of women in each group with a prior history of miscarriage, the early pregnancy loss rate was 11.1% (4 of 36 pregnancies) in the metformin group, as compared with 58.3% (7 of 12 pregnancies) in the control group ($P = 0.002$).

Metformin administration during pregnancy reduces first-trimester pregnancy loss in women with the polycystic ovary syndrome. (*J Clin Endocrinol Metab* 87: 524–529, 2002)

POLYCYSTIC OVARY SYNDROME is the most common form of female infertility in the United States, and it affects 5–10% of women of reproductive age (1, 2). In addition to difficulty conceiving, women with polycystic ovary syndrome are at increased risk of miscarriage after either spontaneous or assisted conception. Rates of early pregnancy loss, defined as miscarriage during the first trimester, are reported to be 30–50% in women with polycystic ovaries (3, 4) or the polycystic ovary syndrome (5–7), which is 3-fold higher than the rate of 10–15% reported in retrospective studies for normal women (8, 9). Keeping in mind that these were retrospective case studies of clinically recognized pregnancies, the true miscarriage rates for both women with polycystic ovary syndrome and normal women were likely underestimated. Conversely, 36–82% of women with recurrent early pregnancy loss are reported to have polycystic ovary syndrome (4, 9–11).

Previous studies have suggested that women who hypersecrete LH, a frequent feature of the polycystic ovary syndrome, are at increased risk for miscarriage after either spontaneous or assisted conception (5, 6). However, it was recently reported that suppression of endogenous LH release before conception, in women with elevated circulating LH concentrations and a history of recurrent miscarriage, did not improve the live birth rate (12). Other reported risk factors for early pregnancy loss in the polycystic ovary syndrome include obesity (13) and elevated serum androgen concentrations (14, 15). Obesity is characterized by insulin resistance with compensatory hyperinsulinemia (*i.e. hyper*insulinemic insulin resistance), and a recent study implicates hyperin-

sulinemia as an independent risk factor for early pregnancy loss (13).

Hyperinsulinemic insulin resistance is also a key feature of the polycystic ovary syndrome (16, 17), and evidence suggests that hyperinsulinemia plays a pathogenic role in the disorder by increasing circulating ovarian androgen concentrations and impeding ovulation. Administration of various insulin sensitizing drugs, such as metformin (18–21), troglitazone (22, 23), and D-*chiro*-inositol (24), have been shown to decrease serum androgen concentrations and to increase ovulation rates in affected women.

Because metformin has beneficial effects on several risk factors for miscarriage in the polycystic ovary syndrome (namely: hyperinsulinemic insulin resistance, hyperandrogenemia, and obesity), we hypothesized that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy in women with the disorder would reduce the rate of early pregnancy loss. To test the hypothesis, we conducted a retrospective study of all women with polycystic ovary syndrome who were seen in an academic endocrinology clinic within the past 4.5 yr and who became pregnant during that time. Specifically, we compared the pregnancy outcomes of the women who became pregnant while taking metformin and remained on metformin throughout pregnancy *vs.* the pregnancy outcomes of the women who did not take metformin during pregnancy.

Materials and Methods

Study subjects

We examined the records of all 96 nondiabetic women with the polycystic ovary syndrome who became pregnant while being seen in the Endocrinology Clinic of the Hospital de Clinicas Caracas between

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Abbreviations: EPL+, Previous history of early pregnancy loss; EPL−, no previous history of early pregnancy loss; hCG, human CG.

January 1996 and June 2000, and who either did not receive metformin at the time of conception or during pregnancy (control group; n = 31) or became pregnant while taking metformin and continued taking metformin at a dose of 1000–2000 mg daily throughout pregnancy (metformin group; n = 65). Polycystic ovary syndrome was defined by the presence of oligomenorrhea (8 or fewer menstrual periods in the last year) and hyperandrogenemia (elevated serum total or free T concentration). Ultrasonography of the ovaries revealed polycystic ovaries in all women, as defined by an ovarian volume more than 9 ml, the presence of 10 or more cysts of 2- to 8-mm diameter, and increased density of stroma (25). All women had normal serum TSH, PRL, and 17α-hydroxyprogesterone concentrations. None of the women had diabetes mellitus, as determined by a 2-h oral glucose tolerance test (26).

It was the standard of care for this practice to assess all women who miscarried in the study for risk factors for miscarriage. The women had normal peripheral blood karyotypes, as did their partners, and had normal uterine anatomy, demonstrated by ultrasonography. All women tested negative for the antiphospholipid syndrome, with negative titers for lupus anticoagulant and anticardiolipin IgG and IgM antibodies. Thyroid function tests were normal, and anti-Tg and thyroid antimicrosomal antibody titers were negative.

The retrospective study was approved by the Internal Review Boards of the Hospital de Clinicas Caracas and Virginia Commonwealth University. The study analyzed existing clinical data, and no patient identifiers were used; therefore, it was exempt from patient consent.

Assessments of subjects

Clinical care was provided to the patients by a single endocrinologist (D. J. Jakubowicz), who used metformin to facilitate fertility or as chronic therapy in the polycystic ovary syndrome, and whose practice it is to continue metformin administration throughout pregnancy. All women were offered metformin to facilitate pregnancy, and women in the control group either elected not to use metformin or discontinued using metformin before conception because of side effects of the drug (diarrhea or gastrointestinal distress). A baseline (before metformin, if given, and prepregnancy) 75-g dextrose oral glucose tolerance test was performed in all women, with determinations of serum insulin and glucose at 0, 60, and 120 min.

Determination of pregnancy. Pregnancy was confirmed by a urine pregnancy test or plasma β-human CG (β-hCG) more than 50 IU/liter and by detection of a gestational sac in the uterine cavity, by ultrasonography. Principal ultrasonographic determinants of pregnancy outcome were also assessed, including maximum gestation-sac diameter, crown-rump length, and embryonic heart rate.

Evaluation during first trimester. Once pregnancy was confirmed, all women repeated the 75-g oral glucose tolerance test between the 4th and 6th weeks of pregnancy, and some women (30 in the metformin group and 15 in the control group) also had blood drawn for serum free T determinations. Early pregnancy ultrasound evaluations were repeated every 2 wk.

Determination of miscarriage. Whenever the ultrasonographic evaluation suggested a poor prognosis for pregnancy outcome, or women had symptoms suggestive of miscarriage (*e.g.* vaginal bleeding, abdominal pain), additional β-hCG and progesterone determinations were performed. Miscarriage was documented by a negative pregnancy test or hCG less than 50 IU/liter and confirmed by uterine ultrasonography.

Methods and assays

Hormonal determinations were performed by the Clinical Endocrinology Laboratory of the Hospital de Clinicas Caracas. The interassay coefficient of variation for the insulin assay (Diagnostic Products, Los Angeles, CA) was 7.6%; and for the progesterone (Diagnostic Systems Laboratories, Inc., Webster, TX) and free T (Diagnostics Systems Laboratories, Inc.) assays, it was 7.4–10%. Serum β-hCG was determined by the IMX microparticles enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). Ultrasonography was performed using an integrated pulsed Doppler (Voluson 530D; Kretz Technik, Zipf, Austria).

Statistical analysis

The women were divided into two groups: 1) the metformin group (*i.e.* women who had received metformin throughout pregnancy; n = 65); and 2) the control group (*i.e.* women who had not received metformin during pregnancy; n = 31). The chi-square test was used to compare the differences in early pregnancy rates between the two groups. In instances where the observed proportion was less the 0.20, Fisher's exact test was used instead. To compare baseline or first-trimester variables between groups, we first tested for normality with the Wilk-Shapiro test and then used Student's two-tailed unpaired *t* test. Results are reported as means ± SE. $P < 0.05$ was considered significant.

Results

History of previous pregnancy outcomes

With regard to previous pregnancy outcomes, 48 of the 65 women in the metformin group had a history of at least 1 prior pregnancy, whereas 17 women were nulliparous. None of the women had received metformin during these previous pregnancies. Among the 48 women in the metformin group with a history of prior pregnancy, there were a total of 75 pregnancies, which resulted in 22 live births and 53 miscarriages, yielding a miscarriage rate of 70.7%.

In the control group, 21 of the 31 women had a history of at least 1 prior pregnancy, whereas 10 women were nulliparous. Among the 21 women in the control group with a history of prior pregnancy, there were a total of 24 pregnancies, which resulted in 11 live births and 13 miscarriages, yielding a miscarriage rate of 54.2%.

TABLE 1. Baseline characteristics before conception of women with polycystic ovary syndrome who either received (metformin group) or did not receive (control group) metformin during pregnancy[a]

Characteristic	Metformin group (n = 65)	Control group (n = 31)	P value
Mean age (yr)	29.5 ± 3.7	30.0 ± 3.2	0.50
Body mass index (kg/m^2)	27.1 ± 1.7	26.9 ± 0.4	0.72
Fasting serum glucose (mg/dl)	89.0 ± 7.0	88.8 ± 8.1	0.92
Fasting serum insulin (μU/ml)	19.2 ± 6.5	18.8 ± 4.9	0.77
Fasting serum glucose to insulin ratio (mg · ml/dl · μU)	5.2 ± 0.2	5.0 ± 0.3	0.62
Serum free testosterone (ng/dl)	3.6 ± 0.2	3.4 ± 0.3	0.33
Proportion who received clomiphene citrate (%)	41.5	29.0	0.34
Proportion who received hCG (%)	9.2	9.7	1.00

[a] Normally distributed data are reported as means ± SEM and were analyzed using the *t* test. Proportional data were compared by the chi-square test or Fisher's exact test and are reported as the observed proportions in percentages.

FIG. 1. Stratification of women with polycystic ovary syndrome who received or did not receive metformin during pregnancy. Represented are all nondiabetic women with polycystic ovary syndrome who received their medical care at a single academic endocrinology practice, over a 4.5-yr period, and who became pregnant during that time period.
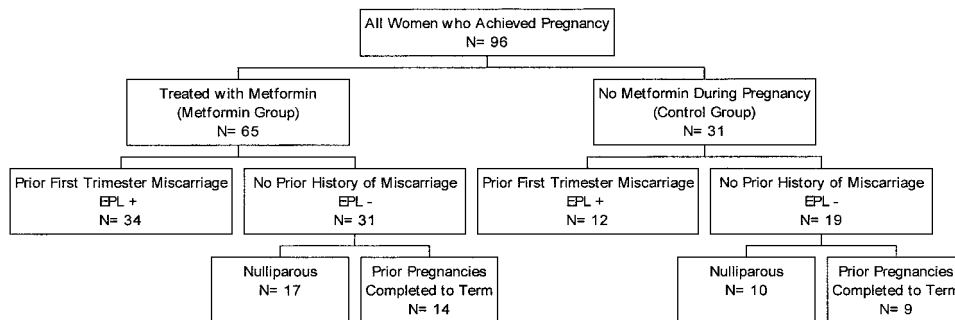
Baseline characteristics

Table 1 describes the baseline anthropometric and hormonal variables for the metformin and control groups, which did not differ with respect to age, body mass index, fasting serum glucose and insulin concentrations, fasting serum glucose-to-insulin ratio, serum free T concentration, and treatment with either clomiphene citrate or hCG for ovulation induction.

Stratification of groups

Stratification of the women is depicted in Fig. 1. The women in each of the two groups were stratified into 2 subgroups: 1) women with previous history of early pregnancy loss (EPL+); and (2) women with no history of previous miscarriage (EPL−). The women who were EPL− were either nulliparous women or women with previous pregnancies completed to term. Of the 65 women in the metformin group, 34 (52.3%) were in the EPL+ group and 31 (47.7%) were in the EPL− group (17 women were nulliparous, and 14 had been previously pregnant). Of the 31 women in the control group, 12 (38.7%) were in the EPL+ group and 19 (61.3%) were in the EPL− group (10 women were nulliparous, and 9 women had been previously pregnant).

Early pregnancy loss

Rates of early pregnancy loss, defined as loss of a conception during the first 12 wk of pregnancy, are described in Table 2. Among the 65 women who had received metformin throughout pregnancy, there were a total of 68 pregnancies (3 women had each conceived twice while on metformin), of which 6 (8.8%) ended in early pregnancy loss. In contrast, among the 31 women in the control group, there were a total of 31 pregnancies, of which 13 (41.9%) ended in early pregnancy loss. The difference in early pregnancy loss rates between the metformin and control groups was significant ($P <$ 0.001; power = 0.97).

Further analysis showed that among women in the 2 EPL+ groups, the early pregnancy loss rate was 11.1% (4 of 36 pregnancies) in the metformin group *vs.* 58.3% (7 of 12 pregnancies) in the control group (P = 0.002; power = 0.90).

EPL− women who were treated with metformin experienced an early pregnancy loss rate of 6.3% (2 of 32 pregnancies) compared with a 5-fold higher early pregnancy loss rate of 31.6% (6 of 19 pregnancies) in the control group (P = 0.04).

TABLE 2. Rates of early pregnancy loss among women with polycystic ovary syndrome who either received (metformin group) or did not receive (control group) metformin during pregnancy[a]

Cohort	Early pregnancy loss rate		P value
	Metformin group[b] (n = 65)	Control group (n = 31)	
All women	8.8% (6/68)	41.9% (13/31)	<0.001
EPL+ women	11.1% (4/36)	58.3% (7/12)	0.002
EPL− women	6.3% (2/32)	31.6% (6/19)	0.04

[a] EPL−, Women with no prior history of miscarriage (either nulliparous women or women with pregnancies completed to term).

[b] Among the 65 women in the metformin group, there were a total of 68 pregnancies. Of these, 36 pregnancies occurred in the context of a history of prior miscarriage, and 32 pregnancies occurred in the context of no previous miscarriage.

However, because of the limited number of subjects in this group, the power of the observation is low (power = 0.66).

Serum insulin and glucose at baseline and during pregnancy

As noted in Table 3, the area under the serum insulin curve at baseline (before conception) was significantly greater in the metformin group, compared with the control group (14.2 ± 0.6 *vs.* 11.2 ± 1.0 mU/ml/min; P = 0.01). In contrast, during the first trimester of pregnancy, the area under the serum insulin curve in the metformin group was significantly lower, compared with the control group (10.0 ± 0.3 *vs.* 13.3 ± 0.4 mU/ml/min; $P <$ 0.001). In the control group, the area under the serum insulin curve had increased from baseline to first-trimester pregnancy by 1.8 ± 0.9 mU/ml·min; whereas, in the metformin group, it decreased by 4.9 ± 0.5 mU/ml·min; the changes in this variable differed significantly between the two groups ($P <$ 0.001).

At baseline, the area under the serum glucose curve did not differ between the metformin and control groups (15,593 ± 286 *vs.* 14,505 ± 481 mg/dl·min; P = 0.06). In contrast, during the first trimester of pregnancy, the area under the serum glucose curve in the metformin group was significantly lower, compared with the control group (13,346 ± 134 *vs.* 15,803 ± 193 mg/dl·min; $P <$ 0.001).
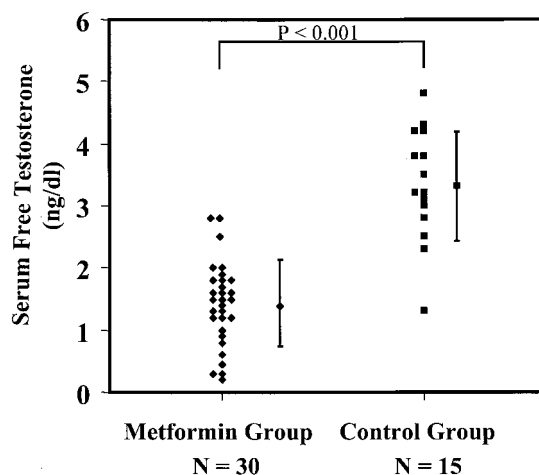
Serum androgens during pregnancy

Serum free T concentrations did not differ between the metformin and control groups at baseline (P = 0.33; Table 1). Serum free T concentrations were again determined between 6–10 wk gestation in 30 of the 65 women in the metformin

TABLE 3. Areas under the serum insulin and glucose curves during an oral glucose tolerance test among women with polycystic ovary syndrome who either received (metformin group) or did not receive (control group) metformin during pregnancy

	Metformin group (n = 65)		Control group (n = 31)		P value[a]
	Baseline	During pregnancy	Baseline	During pregnancy	
AUC insulin (mU/ml · min)	14.2 ± 0.6	10.0 ± 0.3	11.2 ± 1.0	13.3 ± 0.4	<0.001
AUC glucose (g/dl · min)	15.6 ± 0.3	13.3 ± 0.1	14.5 ± 0.5	15.8 ± 0.2	<0.001

AUC, Area under the curve.
[a] For the comparison of the change in the metformin group to the change in the control group.

FIG. 2. Serum free T concentrations during the first trimester of pregnancy in women with polycystic ovary syndrome who received (metformin group) or did not receive (control group) metformin during pregnancy. For each group, individual data and mean ± SD are presented.

group and in 15 of the 31 women in the control group (Fig. 2). In these women, mean first-trimester serum free T concentrations were significantly lower in the metformin group (n = 30), compared with the control group (n = 15) (1.42 ± 0.12 *vs.* 3.32 ± 0.24 ng/dl, respectively; P < 0.001).

Fetal outcome

In the metformin group, 62 pregnancies resulted in live births. Of these, 53 were term deliveries and 8 were preterm (<37 wk). All babies were normal neonates with appropriate size for gestational age. Only one baby, delivered at term, demonstrated a fetal abnormality, and this was achondrodysplasia.

In the control group, 18 pregnancies resulted in live births. Of these, 12 were term deliveries and 6 were preterm. No fetal abnormalities occurred in the placebo group.

Discussion

When women with polycystic ovary syndrome finally achieve pregnancy (often after a long, arduous, and expensive course of fertility treatments), they are faced with the distressing prospect of a substantially increased risk for miscarriage during the first trimester (5–7). The findings of this study support the hypothesis that decreasing hyperinsulinemic insulin resistance, with metformin, in women with the polycystic ovary syndrome, decreases the rate of early pregnancy loss. When metformin was administered throughout pregnancy to women with the disorder, the rate of early

pregnancy loss was decreased dramatically, compared with women who had not received metformin (8.8% *vs.* 41.9%). The early pregnancy loss rate of 8.8% in the metformin group is especially remarkable, given that the historical miscarriage rate for these same women, when they had not been treated with metformin, was 70.6%.

The early pregnancy loss rate in the control group (41.9%) is comparable with the 30–50% rate described in the literature for women with polycystic ovary syndrome (5–7) or polycystic ovaries (3, 4). In contrast, the rate of early pregnancy loss of 8.8% in the women treated with metformin is similar to the rate of 10–15% reported for clinically recognized pregnancies in normal women (8, 9), suggesting that metformin treatment removed any independent risk for early pregnancy loss conferred by the disorder itself. Moreover, our results are similar to those of a pilot study, which recently reported an early pregnancy loss rate of 11% in 19 women with polycystic ovary syndrome treated throughout pregnancy with metformin (27).

Women with polycystic ovary syndrome often have a history of recurrent or habitual (2 or more) abortion, and women with a history of habitual abortion seem to be at an even greater risk for early pregnancy loss than primigravida women with the disorder (4, 8–11). Therefore, it is noteworthy that the women with a history of habitual abortion who were treated with metformin experienced only a 11.8% rate of early pregnancy loss (*i.e.* an 80% decrease in the rate of early pregnancy loss, when compared with the 58.3% observed in comparable women who did not receive metformin).

The idea that metformin improved insulin sensitivity during pregnancy is supported by the following findings. Glucose tolerance before conception was similar in the metformin and control groups. Insulin sensitivity is known to decrease during pregnancy, and this pregnancy-induced insulin resistance was evidenced in the control group by the increase in insulin release during an oral glucose tolerance test. In marked contrast, insulin sensitivity seemed to have improved in the metformin group during pregnancy, as demonstrated by decreases in both the glycemic and insulin excursions during oral glucose tolerance testing.

Metformin administration may have decreased the rate of early pregnancy loss by several potential mechanisms. Elevated serum androgen concentrations have been reported to be a risk factor for early pregnancy loss in the polycystic ovary syndrome (14, 15), and the women who received metformin had serum free T levels, at 6–10 wk of pregnancy, that were 57% lower than those in the women who did not receive metformin. This finding is consistent with a case reported by Sarlis *et al.* (28), in which a woman with hyperthecosis and elevated serum T concentrations during pregnancy re-

sponded to metformin therapy with a marked reduction in circulating T and delivered a healthy, nonvirilized baby girl.

In addition, mechanisms other than androgen reduction may also have played a role in metformin's apparent effects to protect against miscarriage. For example, metformin's salutary effects may have been related directly to its action to improve insulin sensitivity in the polycystic ovary syndrome (18, 29). A recent study implicates insulin resistance as an independent risk factor for early pregnancy loss in women with polycystic ovary syndrome (13), and a report suggests that hyperinsulinemia adversely affects endometrial function and the periimplantation environment by decreasing expression of glycodelin and IGF binding protein-1 (30). Glycodelin may play a role in inhibiting the endometrial immune response to the embryo (31, 32), and IGF binding protein-1 seems to facilitate adhesion processes at the feto-maternal interface (33, 34).

Furthermore, plasma plasminogen activator inhibitor-1 concentrations are increased in insulin-resistant states, including the polycystic ovary syndrome (35, 36). Increased plasminogen activator inhibitor-1 activity is an independent risk factor for miscarriage in the polycystic ovary syndrome (37, 38), presumably because it induces a hypofibrinolytic state. Metformin administration has been reported to decrease circulating plasminogen activator inhibitor-1 in women with polycystic ovary syndrome (39, 40).

Numerous studies have demonstrated that insulin-sensitizing drugs reduce hyperinsulinemia, improve ovulation, and decrease serum T concentrations in women with the polycystic ovary syndrome (18–24). However, of the commercially available drugs, only metformin has a reassuring safety profile for use during pregnancy. Metformin is classified as a category B drug, which means that no teratogenic effects have been demonstrated in animal studies. It was administered in South Africa to a limited number of women with type 2 diabetes mellitus or gestational diabetes throughout their pregnancies, and no teratogenic effects or adverse fetal outcomes were reported (41–43). In our study, there were no adverse fetal outcomes noted among the women treated with metformin, except for one infant born with achondrodysplasia, which is an inherited disorder unlikely to be related to metformin therapy.

In summary, administration of metformin to pregnant women with polycystic ovary syndrome throughout pregnancy was associated with a marked and significant reduction in the rate of early pregnancy loss. This beneficial effect of metformin administration was also noted in affected women with an established history of miscarriage. Except for a single baby born with achondrodysplasia, metformin was not associated with any adverse fetal outcomes. The findings of this retrospective study of a single endocrine clinic's clinical experience suggests that a randomized placebo-controlled trial is warranted to confirm metformin's action to decrease the rate of early pregnancy loss in women with polycystic ovary syndrome.

Acknowledgments

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