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Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study

C. J. Glueck, M.D., Harvey Phillips, M.D., Dan Cameron, M.D., Luann Sieve-Smith, B.A., and Ping Wang, Ph.D.

The Cholesterol Center, Jewish Hospital, Cincinnati, Ohio

Objective: To determine whether metformin would safely reduce the rate of first-trimester spontaneous abortion without teratogenicity in 19 women with the polycystic ovary syndrome (PCOS).

Design: Prospective pilot study.

Setting: Outpatient.

Patient(s): Twenty-two previously oligoamenorrheic, nondiabetic women with PCOS; 125 women with PCOS who were not currently pregnant and who had ≥1 previous pregnancy while they were not receiving metformin.

Intervention(s): Metformin, 1.5–2.55 g/day, throughout pregnancy.

Main Outcome Measure(s): Rates of first-trimester spontaneous abortion and teratogenicity.

Result(s): Before metformin, 10 women had 22 previous pregnancies with 16 first-trimester spontaneous abortions (73%). While receiving metformin, these 10 women had 6 normal live births (60%), 1 spontaneous abortion (10%), and 3 normal ongoing pregnancies (30%) (all ≥13 weeks; median gestation, 23 weeks). Among women receiving metformin, including those with live births and normal pregnancy for at least the first trimester, 1 of 10 (10%) had first-trimester spontaneous abortion compared with 73% in 22 previous pregnancies without metformin ($P<.002$). To date, the 19 women receiving metformin have had no adverse maternal side effects, and no birth defects have occurred; 9 (47%) had normal term live births, 2 (11%) had normal and appropriate for gestational age births (one at 33 and one at 35 weeks), 6 (32%) have ongoing normal pregnancies lasting longer than the first trimester, and 2 (10.5%) had first-trimester spontaneous abortions. Sonography showed normal fetal development without congenital defects in the 6 ongoing pregnancies (median gestation, 23 weeks). Among women who received metformin before conception, reductions in insulin and plasminogen activator inhibitor activity were correlated ($r=0.65$, $P=.04$).

Conclusion(s): Metformin therapy throughout pregnancy in women with PCOS reduces the otherwise high rate of first-trimester spontaneous abortion seen among women not receiving metformin and does not appear to be teratogenic. (Fertil Steril® 2001;75:46–52. ©2001 by American Society for Reproductive Medicine.)

Key Words: Metformin, pregnancy, polycystic ovary syndrome, teratogenicity

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Reprint requests: C. J. Glueck, M.D., The Cholesterol Center, Jewish Hospital, ABC Building, 3200 Burnet Avenue, Cincinnati, Ohio 45229 (FAX: 513-585-7950; E-mail: glueckch@healthall.com).

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The polycystic ovary syndrome (PCOS) is characterized by oligoamenorrhea and clinical and biochemical hyperandrogenism (hirsutism, severe acne, and high serum levels of testosterone, androstenedione, and DHEAS) (1–3). Many women with PCOS have anovulatory infertility, insulin resistance or hyperinsulinemia, and morbid obesity. Although not generally accepted yet as a classic marker of PCOS, we (1–3) and some other investigators (4–6) (but not all [(7)]) found high levels of the major inhibitor of fibrinolysis, plasminogen activator inhibitor (PAI) activity. In a recent study of 43 amenorrheic women with PCOS, the insulin-sensitizing drug metformin, 1.5–2.55 g/day for 6.1 months, reduced endocrinopathy in PCOS by reducing hyperinsulinemia-driven hyperandrogenism; normal menses resumed in 91% of women (1).

Without metformin therapy, women with

PCOS are frequently infertile (1–3); 44% of those who become pregnant miscarry in the first trimester (2). To elucidate the causes of miscarriage in women with PCOS, we previously performed a retrospective study of pregnancy outcomes in 41 women with PCOS who were not taking metformin and had 1 or more pregnancies (2). These 41 women had 77 pregnancies that resulted in 34 miscarriages (44%) and 42 live births (55%). Hypofibrinolytic PAI activity was independently and positively associated with miscarriage (2). In three nonoverlapping pregnancy outcome groups (worst, intermediate, best), PAI activity was positively associated with the worst pregnancy outcomes ($P=.05$) (2).

Gris et al. (8, 9) reported high levels of PAI activity in two studies of 116 and 500 women who had early recurrent miscarriages of unknown origin. They speculated that "an impaired plasmin dependent proteolysis in women might favor recurrent abortion by promoting early placental circulation or by limiting trophoblast development, or both (8)." Because high PAI activity promotes miscarriage (2), probably through thrombotic induction of placental insufficiency (8, 9), and because metformin lowers PAI activity (3, 10–13), we previously speculated that metformin therapy during pregnancy would reduce the otherwise high rate of first-trimester spontaneous abortion in women with PCOS (2, 12, 13).

Because metformin therapy produces regular normal menstrual cycles in 91% of previously infertile oligoamenorrheic women with PCOS (1), most of whom want very much to conceive, many pregnancies are now occurring in women with PCOS who conceived while taking metformin (12). This trend raises the question of the effects of continuation of metformin therapy throughout pregnancy. Although Coetzee and Jackson (14–18) reported that metformin was not teratogenic and did not have a negative impact on fetal outcome and although metformin is classified as a class B drug by the U.S. Food and Drug Administration, our anecdotal experience is that metformin therapy is usually discontinued during pregnancy in women with PCOS who conceived while receiving the drug.

In this pilot study, we sought to determine whether metformin would safely reduce the rate of first-trimester spontaneous abortion without producing teratogenicity in 19 women with PCOS who conceived while receiving metformin and continued therapy throughout pregnancy.

MATERIALS AND METHODS

Patients

We used a protocol approved by the Institutional Review Board of Jewish Hospital. All patients gave signed informed consent. The diagnosis of PCOS was made on the basis of chronic oligoamenorrhea, clinical and biochemical hyperandrogenism (hirsutism, severe acne, and high levels of total or free testosterone, androstenedione, and DHEAS), and exclusion of the following diseases: hypothyroidism (normal levels of thyroxine and thyroid-stimulating hormone), hyperprolactinemia (normal serum prolactin level), and congenital adrenal hyperplasia (normal 17-hydroxyprogesterone level). Ancillary diagnostic criteria for PCOS were polycystic ovaries on ultrasonography, presence of acanthosis nigricans, and luteinizing hormone-to-follicle-stimulating hormone ratio ≥ 2. Polycystic ovaries were identified by the presence of ≥ 10 subcapsular follicles 2–8 mm in diameter on pelvic ultrasonography (1–3, 11, 19).

Oligomenorrhea was defined as ≤ 6 menses per year; amenorrhea was defined as no menses for 1 year. Hyperinsulinemia was identified as a fasting serum insulin level that was at least the 95th percentile of the normal control value (20 μ/mL). The presence of hyperinsulinemia was not obligatory for the diagnosis of PCOS, nor was it required for entry into the study. As in our previous studies (1–3, 11), exclusion criteria were serum creatinine level >1.5 mg/dL, pituitary insufficiency, and type 1 or 2 diabetes mellitus. Women taking estrogen-progestin oral contraceptives or drugs known to effect endogenous sex hormones were also excluded.

Study Protocol

Our open-label, consecutive case series study conducted at a single center included 22 women with PCOS (Table 1) from the midwestern United States who were referred for metformin therapy for PCOS (1). These women were selected from a previously studied cohort of 118 oligoamenorrheic, hyperandrogenemic women with PCOS who received metformin (1, 2, 13). We consecutively enrolled the patients in the current study as they became pregnant. Our study had no selection bias in terms of previous pregnancy or spontaneous first-trimester abortion.

The 22 women were prospectively followed in Cincinnati or in their home towns, under our direction and using our protocol. Before conception, patients were evaluated every 2 months with serial measurements of fasting serum insulin, PAI activity, and serum sex hormones. All women conceived while receiving metformin, 1.5 to 2.55 g/day; 19 continued to receive metformin throughout pregnancy and 3 stopped therapy when pregnancy was first detected (4–6 weeks of gestation) (Table 2). Patients made one follow-up visit per month throughout pregnancy; all pregnancies were followed by using a high-risk pregnancy protocol (20) and all women took prenatal vitamins that contained folic acid, 1 mg/day.

Pregnancy outcomes in a group of 125 women with PCOS who were not currently pregnant and who had ≥ 1 previous pregnancy while not receiving metformin were retrospectively assessed. This group is an expansion of our previous preliminary report on 118 women with PCOS (13).

TABLE 1

Pre-treatment characteristics of 22 patients with the polycystic ovary sydrome who conceived while receiving metformin.

Patient	Oligo-amenorrhea	Ferriman-Gallwey score	Acne	Acanthosis nigricans	PCOS by ultrason-ography	Body weight (lb)	Quetelet (kg/cm^2 × 1,000)	Insulin level (μ/mL)	PAI-1 gene poly-morphism	PAI activity (U/mL)
Normal range	Regular	<7	No	No	−		<LCR 95th	<20 UU/mL	5G5G	≤18.2 U/mL
1	O	4	Yes	No	+	155	2.47	12	4G4G	0.4
2	O	7	Yes	No	+	165	2.67	10	4G5G	58.9
3	O	8	No	No	+	138	2.10	7	4G4G	13.8
4	A	12	Yes	No	+	224	3.39[a]	32	5G5G	25.3
5	O	7	No	No	+	179	2.94	11	4G4G	8.4
6	A	12	Yes	No	+	224	3.34[a]	58	4G4G	55.1
7	O	12	Yes	No	+	147	2.45	12	5G5G	19.4
8	A	8	No	No	+	194	2.77	17	4G5G	15.3
9	O	16	Yes	No	+	228	3.58[a]	29	4G4G	31.1
10	O	11	Yes	No	+	169	3.07	18	4G5G	25.8
11	O	12	Yes	No	+	230	3.99[a]	75	4G4G	27.7
12	A	12	No	No	ND	256	4.20[a]	52	4G5G	49.8
13	O	8	Yes	Yes	+	202	3.37[a]	40	5G5G	24.8
14	A	13	No	No	+	207	3.30[a]	25	4G5G	15.3
15	O	7	No	No	+	192	3.20	18	4G5G	3.2
16	A	8	No	No	+	209	3.59[a]	25	—	—
17	A	8	Yes	No	+	189	3.41[a]	6	4G4G	9.1
18	A	8	Yes	Yes	+	262	4.80[a]	23	4G4G	10.5
19	A	17	Yes	No	+	148	2.34	15	4G5G	9.2
20	Regular	18	Yes	No	ND	218	3.81[a]	33	4G5G	19.0
21	O	19	No	Yes	+	118	1.97	8	5G5G	2.9
22	A	12	Yes	No	+	206	3.60[a]	29	4G5G	19.5
Mean (±SD)						194 ± 38		25 ± 18		21 ± 16
Median						198		21		19

Note: ND = not done; PAI = plasminogram activator inhibitor; PCOS = polycystic ovary syndrome.

[a]Quetelet index >LRC 95th percentile.

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Normal controls

Levels of PAI activity in 23 healthy normal age-matched control women (21) were compared to preconception levels in the 22 women with PCOS studied at Jewish Hospital. Hypofibrinolytic 4G polymorphism of the *PAI-1* gene in the 22 patients with PCOS was compared with that in 109 healthy normal women (21).

Study Limitations

An optimal study design of the efficacy and safety of metformin throughout pregnancy in women with PCOS would be a randomized, placebo-controlled, double-blind, clinical trial. However, to design and successfully carry out such a trial, efficacy and safety data must first be collected to allow construction of power and sample size estimates. Because no data have previously been published on the efficacy or safety of metformin throughout pregnancy in women with PCOS, power and sample size estimates for such studies cannot be constructed without accrual of the nonblinded, open-label pilot data found in this study.

In the present study, because our patients had histories of habitual infertility (1, 3) before metformin therapy, comparisons of current pregnancy outcomes during receipt of metformin with outcomes of previous pregnancies achieved without metformin therapy (Table 2, Figure 1) may be exaggerated owing to the small sample. Our ability to discern teratogenicity was also necessarily limited by the small sample. Because the major focus of our study was first-trimester spontaneous abortion, not every woman has been followed through the end of pregnancy to date.

Laboratory Methods

At study entry, fasting levels of serum insulin (1), PAI activity (2), and 4G polymorphism of the *PAI-1* gene (21) were measured by using previously reported methods before metformin therapy in the 22 women with PCOS. Fasting serum insulin and PAI activity were remeasured every 2 months while these women were receiving metformin and before they had conceived . Outcome measures in the 22 women with PCOS were the number of first-trimester spontaneous abortions, number of birth and intrauterine defects, and the nature and rate of intrauterine fetal development according to sonography.

TABLE 2

Pregnancy outcomes in women who conceived while receiving metformin and continued therapy throughout pregnancy or stopped therapy at 4–6 weeks' gestation.

	Current pregnancy							Previous pregnancies without metformin		
				Ongoing						
					Weeks of gestation					
Group	No. of patients	No. of live births	No. of first trimester spontaneous abortions	No. of patients	Mean (±SD)	Median	No. of women ≥13 weeks	No. of pregnancies	No. of live births (%)	No. of first trimester spontaneous abortions (%)
Did not stop metformin therapy	19	11	2	6	26 ± 6	23	6			
Did not stop metformin therapy and had previous pregnancies	10	6	1	3	26 ± 8	23	3	22	6 (27)	16 (73)
Stopped metformin at 4–6 weeks of pregnancy	3	2 (1 patient foramen ovale)	1					4[a]	2 (50)	2 (50)

[a] One elective abortion was excluded.

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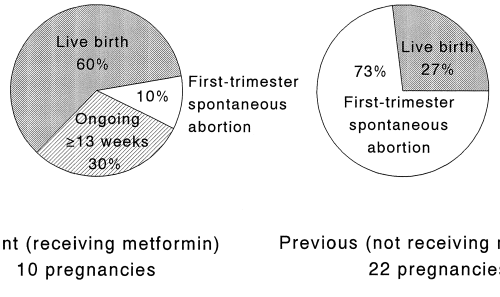
Statistical Analysis

Chi-square analyses and Fisher exact tests (when cell size was <5) were done to compare outcomes during receipt and nonreceipt of metformin and to compare women with PCOS with normal controls. Wilcoxon nonparametric tests of difference were used to compare PAI activity in the 22 PCOS women with that in normal controls. Spearman nonparametric correlations were calculated among fasting serum insulin level, PAI activity, and 4G polymorphism of the *PAI-1*gene in the 22 PCOS women before metformin therapy. Spearman correlations were calculated between changes in insulin level and PAI activity in women before conception and while receiving metformin.

In the 115 of 125 women with PCOS and ≥1 previous pregnancy achieved while not receiving metformin for whom data were complete, stepwise logistic regression was done to assess risk factors for fetal loss. Explanatory variables were age, serum levels of testosterone and androstenedione, Quetelet index, *PAI-1* gene polymorphism (2), fasting serum insulin level, PAI activity, and number of pregnancies. The dependent variable was live birth vs. no live birth. All statistical analyses were performed by using SAS software (22).

FIGURE 1

Current (during metformin therapy) and previous (while not receiving metformin) first-trimester spontaneous abortions and live births in 10 women with the polycystic ovary syndrome who had 22 previous pregnancies. $P<.002$, Fisher exact test.



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RESULTS

Characteristics of the 22 Patients with PCOS at Study Entry, Before Metformin Therapy

Ten of the 22 (45%) women with PCOS were amenorrheic, 11 (50%) were oligomenorrheic, and 1 (5%) had regular normal menses (Table 1). Twenty-one (95%) women had clinical hyperandrogenism (hirsutism and Ferriman-Gallwey score ≥7) (23) (Table 1). All 20 women who had pelvic ultrasonography had polycystic ovaries (100%) (Table 1). Of the 22 women, 12 (55%) had Quetelet indices ≥ the Lipid Research Clinic's 95th percentile for age-matched unselected women (24) (Table 1). As a group, the women were morbidly obese (mean [±SD] body weight of 194 ± 38 pounds (Table 1).

TABLE 3

Duration of gestation, height, and weight in neonates whose mothers continued metformin therapy throughout pregnancy and those whose mothers stopped therapy at 4–6 weeks' gestation.

	Mother	Gestation (wk)	Baby's sex	Height (cm)	Height Percentile	Weight (gm)	Weight Percentile	Neonate's status	Birth defects
Continued metformin therapy throughout pregnancy	1	40.0	Male	51	50th	3450	50th	Healthy	None
	3	40.0	Male	56	95th	4449	95th	Healthy	None
	6	40.0	Female	51	75th	3178	50th	Healthy	None
	8	40.0	Female	50	25th	3360	50th	Healthy	None
	9	40.0	Male	52	75th	3360	50th	Healthy	None
	10	38.0	Female	49	25th	2951	25th	Healthy	None
	11	35.0	Female	46	75th	2679	75th	Healthy	None
	16	33.0	Female	42	25th	1998	50th	Healthy	None
	17	40.4	Female	52	90th	3450	50th	Healthy	None
	18	40.0	Female	43	<5th	2906	10th	Healthy	None
	20	40.8	Male	53	90th	4177	90th	Healthy	None
Stopped metformin therapy at 4–6 weeks' gestation	2	41.0	Male	48	10th	3541	50th	Healthy	None
	22	39.0	Female	48	25th	5176	95th	Healthy	Patent foramen ovale

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Pregnancy outcomes

Twenty-two women with PCOS conceived while taking metformin (13 were receiving 1.5 g/day and 9 were receiving 2.55 g/day). Three of the 22 women stopped metformin therapy immediately after documentation of pregnancy (at 4–6 weeks of gestation) (Table 2). The remaining 19 women continued to take metformin throughout their pregnancies; 11 took 1.5 g/day and 8 took 2.55 g/day (Table 2).

Of the 19 women who continued metformin therapy throughout pregnancy, 10 had 22 previous pregnancies while not receiving metformin (Figure 1, Table 2). Of these 22 previous pregnancies without metformin, there were 6 normal live births (27%), 16 (73%) first-trimester spontaneous abortions, and no birth defects (Figure 1, Table 2).When metformin therapy was continued throughout their current pregnancies, these 10 women had 6 normal live births (60%), 1 spontaneous abortion (10%), and 3 ongoing normal pregnancies (all ≥13 weeks) (30%), with a median gestation of 23 weeks (Figure 1, Table 2). Thus, the rate of first-trimester spontaneous abortions was greatly reduced in these women compared with their previous pregnancies, when they were not taking metformin (10% vs. 73%; $P<.002$, Fisher test) (Figure 1, Table 2).

Among the 19 women who continued metformin therapy throughout pregnancy, there have been 11 normal live births without birth defects (58%) (Table 3), 2 first-trimester spontaneous abortions (10.5%), and 6 ongoing normal pregnancies, all ≥13 weeks (32%); median gestation was 23 weeks (Table 2). Sonography showed normal fetal development without congenital defects in the 6 ongoing pregnancies.

Of the 22 women, 3 stopped metformin therapy immediately after confirmation of pregnancy (at 4–6 weeks gestation) (Table 2). These 3 women had 5 previous pregnancies during which they did not take metformin. Excluding 1 elective abortion, of the remaining 4 pregnancies, there were 2 (50%) live births and 2 (50%) first-trimester spontaneous abortions (Table 2). Of these current pregnancies, there have been 2 live births (1 with patent foramen ovale) and 1 first-trimester spontaneous abortion (Table 1). No major adverse maternal side effects from metformin have been observed during pregnancy. Before conception, nausea or diarrhea commonly appeared in the first 2–3 weeks after starting metformin therapy, but these symptoms resolved thereafter.

Gestation, Newborn Height, Weight, Health Status, and Birth Defects

Of the 11 women continuing metformin throughout pregnancy, 2 (11 and 16) had preterm deliveries (<37 weeks) (Table 3). Both healthy normal neonates were appropriate size for gestational age (25, 26) and had no birth defects. Nine of the 11 women who continued metformin therapy throughout pregnancy had term deliveries of normal healthy neonates with normal height and weight (25, 26) and no birth defects. One of these 9 neonates (18) had length below the 5th percentile but weight above the 10th percentile (25, 26). Two healthy neonates with normal height and weight (25, 26) were born at term to women who discontinued metformin therapy at 4–6 weeks of gestation (Table 3). One neonate (22) had a patent foramen ovale.

Plasminogen Activator Inhibitor, Fasting Serum Insulin, and 4G/5G Polymorphism of the *PAI-1* Gene

Before metformin therapy was started, at study entry, fasting serum insulin level was high (27) (≥20 μ/mL) in 11 (50%) of the 22 women and PAI activity was high (≥ 95th percentile in normal persons) in 11 of 21 women for whom this measurement was available (52%) (Table 1). Plasminogen activator inhibtor activity in the 22 women with PCOS before metformin therapy (21 ± 16 U/mL) (Table 1) was higher than that in 23 healthy adult normal control women (7 ± 6 U/mL) (P=.0007). Plasminogen activator inhibitor activity was ≥ the normal 95th percentile (18.2 U/mL) before metformin therapy in 11 of 21 (52%) women with PCOS compared with 4% of 23 normal healthy control women (χ^2=12.8, P=.001).

Before metformin therapy, fasting serum insulin level was positively correlated with PAI activity (r=0.60, P=.004). Over a median treatment period of 6 months before conception, median fasting serum insulin level decreased from 25 to 15 μ/mL in 15 women who had repeated measurement of fasting serum insulin (P=.0071). This reduction in fasting serum insulin during metformin therapy and before conception was positively correlated with reduction in PAI activity (r=0.65, P=.04). Having the 4G/4G genotype was inversely correlated with the reduction in PAI activity during metformin therapy (r=0.65, P=.04).

Of the 21 women who were tested for the hypofibrinolytic 4G/4G polymorphism for the *PAI-1* gene, 8 (38%) had this polymorphism, 9 (43%) had 4G/5G heterozygosity, and 4 (19%) had the normal wild-type genotype (5G/5G). Women with PCOS were marginally more likely than 109 healthy female controls to have the mutant 4G allele (χ^2= 3.4, P=.065).

History of Pregnancy in the Absence of Metformin Therapy in 125 Women with PCOS

There were 265 pregnancies in the 125 women with PCOS who had 1 or more previous pregnancies in the absence of metformin therapy (1, 2, 12, 13). Of these pregnancies, 39% ended in first-trimester spontaneous abortions and 60% resulted in live births. To examine determinants of pregnancy outcomes in the absence of metformin therapy stepwise logistic regression was performed in 115 of 125 women for whom data were complete. Plasminogen activator inhibitor activity was inversely associated with having live births (P=.031), whereas number of pregnancies was positively associated with having live births (P=.027).

DISCUSSION

In our previous study of 41 women with PCOS without metformin therapy (2), only 55% of pregnancies resulted in live infants; 44% ended in first-trimester miscarriages. Hypofibrinolytic PAI activity was found to be a significant independent risk factor for miscarriage (2). We concluded that hypofibrinolysis mediated by PAI activity was an independent, significant, potentially reversible risk factor for pregnancy complications that probably acted through thrombotic induction of placental insufficiency (2). In the present report, in which we expanded our cohort to 125 women with PCOS, 39% of previous pregnancies in which women did not receive metformin resulted in first-trimester spontaneous abortions; PAI activity was inversely and independently associated with the likelihood of live birth. Metformin therapy lowers PAI activity without lowering plasma glucose levels in euglycemic women with PCOS (1, 3, 11) and should therefore reduce the rate of first-trimester spontaneous abortion, as we observed. The presence of high PAI activity in PCOS is a recent finding of ours (1–3) and has been confirmed by some (4–6) but not all (7) other investigators. Before metformin therapy, fasting serum insulin level was correlated with PAI activity, as reported elsewhere (1, 3, 11). We speculate that metformin's ability to lower PAI activity is related to a reduction in fasting serum insulin level and insulin resistance, as reported here and elsewhere (1, 3, 11). We further speculate that the apparent improvement in pregnancy outcomes during metformin therapy that we observed may be related to metformin's effects on insulin, insulin resistance, and PAI activity.

When pregnancies that occurred in the absence of metformin therapy and those that occurred while receiving metformin therapy were compared in the same cohort of women, the rate of first-trimester spontaneous abortion was reduced from a historical value of 73% to 10% (P<.002). Of paramount importance, this reduction was achieved without evident teratogenicity and without major persistent maternal side effects. Of 19 pregnancies during which metformin therapy was continued, there have been 2 first-trimester spontaneous abortions, 11 normal live births without birth defects, and 6 normal ongoing pregnancies, all ≥ 13 weeks and without congenital defects by sonography. The absence of teratogenicity is encouraging but not surprising, given the lack of teratogenicity observed with metformin therapy in previous reports by Coetzee and Jackson (14–18), who studied much larger cohorts of women with type 2 diabetes.

The high rate of first-trimester spontaneous abortion rates in the absence of metformin therapy in women with PCOS, which ranged from 39% in the 125 women with PCOS who had 1 or more previous pregnancies to 50% to 73% in historical controls, is not surprising, given the apparent pathoetiologic role of hypofibrinolytic PAI activity in spontaneous abortion (2, 8, 9, 13) and a similar role of hypofibrinolytic 4G/4G polymorphism of the *PAI-1* gene, a major determinant of PAI activity (28). Plasminogen activator inhibitor activity, the preeminent determinant of hypofibrinolysis, is an independent determinant of spontaneous abortion in women with PCOS (2); it apparently causes placental

insufficiency by reducing lysis of thrombi in the placenta. Plasminogen activator inhibitor activity is much higher in women with PCOS than in normal women, as reported here and elsewhere (1–6, 11). In addition, we and others (1, 2) found that the hypofibrinolytic 4G polymorphism of the *PAI-1* gene is more common in women with PCOS than in normal women. We believe that hypofibrinolytic high PAI activity (8, 9, 11), which is largely reversible with metformin therapy (1, 3, 11), and PAI-1 gene-mediated hypofibrinolysis (28) should join familial and acquired thrombophilia (28–30) as risk factors for major complications of pregnancy.

In our study, patients with PCOS treated with metformin throughout pregnancy appear to have a much improved pregnancy outcome compared with historical outcomes in the same group of women, when they were not receiving metformin. Metformin therapy does not appear to be teratogenic. The results of our pilot study should allow calculation of sample size and power estimates for blinded, placebo-controlled, randomized clinical trials. To further confirm the efficacy and safety of metformin therapy during pregnancy in women with PCOS, long-term follow-up of infants born during such a placebo-controlled clinical trial will be required, and growth and development should be prospectively assessed.

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