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Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin

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BACKGROUND: We sought to determine whether metformin, which had facilitated conception in 72 oligoamenorrhoeic women with polycystic ovary syndrome (PCOS), would safely reduce the rate of first trimester spontaneous abortion (SAB) and increase the number of live births without teratogenicity. METHODS: Seventy-two oligoamenorrheic women with PCOS conceived on metformin (2.55 g/day). They were prospectively assessed in an outpatient clinical research centre. Outcome measures included number of first trimester SAB, live births, normal ongoing pregnancies ≥13 weeks, gestational diabetes (GD), congenital defects (CD), birthweight and height, as well as weight, height, and motor and social development during the first 6 months of life. RESULTS: Of the 84 fetuses, to date there have been 63 normal live births without CD (75%), 14 first trimester SAB (17%), and seven ongoing pregnancies ≥13 weeks with normal sonograms without CD (8%). Previously, without metformin, 40 of the 72 women had 100 pregnancies (100 fetuses) with 34 (34%) live births and 62 (62%) first trimester SAB. In current pregnancies on metformin in these 40 women (46 pregnancies, 47 fetuses), there have been 33 live births (70%), two pregnancies ongoing ≥13 weeks (4%), and 12 SAB (26%) ($P < 0.0001$). There was no maternal lactic acidosis, and no maternal or neonatal hypoglycaemia. Fasting entry serum insulin was a significant explanatory variable for total (previous and current) first trimester SAB, odds ratio 1.32 (for each 5 μU/ml rise in insulin), 95% CI 1.09–1.60 ($P = 0.005$). On metformin, GD developed in 4% of pregnancies versus 26% of previous pregnancies without metformin, $P = 0.025$. There have been no major CD in the 63 live births or CD by sonography in the seven fetuses ≤13 weeks. In the 63 live births, neither weight nor height differed from the normal neonatal population. At 6 month follow-up, height was greater ($P = 0.008$) and weight did not differ from the normal paediatric population; motor and social development were normal. CONCLUSIONS: Metformin therapy during pregnancy in women with PCOS was safely associated with reduction in SAB and in GD, was not teratogenic, and did not adversely affect birthweight or height, or height, weight, and motor and social development at 3 and 6 months of life.

Key words: gestational diabetes/metformin/polycystic ovarian syndrome/pregnancy/spontaneous abortion

Introduction

Polycystic ovary syndrome (PCOS) is characterized by oligoamenorrhoea, clinical and/or biochemical hyperandrogenism, infertility, and, commonly, by insulin resistance, hyperinsulinaemia, and morbid obesity (Kawadzki and Dunaif, 1992; Velazquez *et al*., 1997; Glueck *et al*., 1999b, 2001b,c, 2002; Moghetti *et al*., 2000). The insulin-sensitizing drug, metformin (1.5–2.55 g/day), ameliorates the endocrinopathy of PCOS by reducing hyperinsulinaemia-mediated hyperandrogenism, allowing resumption of predominantly ovulatory normal menses in 55% (Moghetti *et al*., 2000) to 91% (Glueck *et al*., 1999b) of adult women and in 91% of teenage girls (Glueck *et al*., 2001c). Without metformin, spontaneous abortion (SAB) is common in women with PCOS, occurring in 42% of pregnancies (Jakubowicz *et al*., 2002), 39% (Glueck *et al*., 2001b), 44% (Glueck *et al*., 1999a), 73% (Glueck *et al*., 2001b), and 25% (Wang *et al*., 2001). Wang *et al*. (2001) however, suggested that the observed higher SAB in women with PCOS was attributable to their confounding high prevalence of obesity and the types of fertility induction treatment they received.

Because metformin has beneficial effects on risk factors for the high rate of first trimester SAB in PCOS [hyperinsulinaemia, insulin resistance, hyperandrogenaemia, obesity, and high levels of plasminogen activator inhibitor activity (PAI-Fx)] (hypofibrinolytic) (Glueck *et al*., 1999a, 2001; Fedorcsak *et al*., 2000; Jakubowicz *et al*., 2002), metformin should reduce first trimester SAB. Metformin has been reported to lower the rate of first trimester SAB (Glueck *et al*., 2001b; Jakubowicz *et al*., 2002). Ten women with PCOS had 16 first trimester SAB in 22 pregnancies without metformin (73%), while in 10 pregnancies on metformin, there was one SAB (10%), $P < 0.002$ (Glueck *et al*., 2001b). It was postulated that metformin's reduction in PAI-Fx contributed to the reduction in SAB (Glueck *et al*., 2001b). Jakubowicz *et al*. (2002)

retrospectively studied 65 women with PCOS who received metformin during pregnancy and 31 who did not. The early pregnancy loss rate in the metformin group was 6/68 pregnancies (8.8%) compared with 13/31 (41.9%) in the untreated control group ($P < 0.001$). In a subset of women with prior history of miscarriage, the early pregnancy loss rate was 4/36 pregnancies (11.1%) in the metformin group versus 7/12 (58.3%) in the controls ($P = 0.002$).

In the current study, we sought to determine whether metformin, which had facilitated conception in 72 oligoamenorrhoeic women with PCOS, would safely reduce their rate of first trimester SAB and increase the number of live births without producing teratogenicity, and without adversely affecting infants' birthweight or height, or weight, height, and social and motor development during the first 6 months of life.

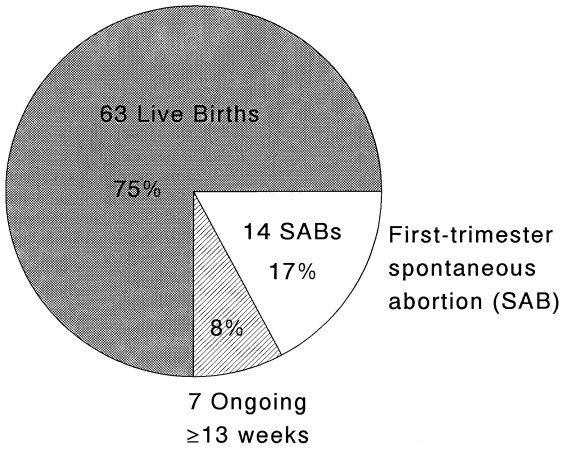

Figure 1. Current pregnancy outcomes in 72 women with polycystic ovarian syndrome on metformin, 81 pregnancies, 84 fetuses (three twin pregnancies, nine women with two singleton pregnancies, 60 women with one singleton pregnancy).

Materials and methods

Patients with PCOS

This work was carried out with a protocol approved by the Jewish Hospital Institutional Review Board. All patients gave signed informed consent. The diagnosis of PCOS was made on the basis of chronic oligoamenorrhoea and either clinical hyperandrogenism [hirsutism (Ferriman and Gallwey, 1961), severe acne] or biochemical hyperandrogenism (high levels of total or free testosterone, androstenedione, or dehydroepiandrosterone sulphate). Exclusion criteria included serum creatinine >1.5 mg/dl, types 1 and 2 diabetes, pituitary insufficiency, persistent hyperprolactinaemia, and congenital adrenal hyperplasia (Glueck *et al*., 1999b).

Study protocol

Our prospective, open label, single centre, consecutive case series study included 72 women from the midwestern USA who were referred for a 1 year study of efficacy and safety of metformin therapy in PCOS and who conceived on metformin, 1.5–2.55 g/day. None of the women, having been offered participation in the metformin treatment study, declined participation. The 72 women were consecutively enrolled in the pregnancy follow-up study after they had conceived, and were prospectively followed in Cincinnati or in their home towns, under our direction, and using our protocol (Glueck *et al*., 2001b). There was no selection bias related to outcome(s) of previous pregnancies without metformin. All pregnancies (historical, current) were conceived with the same partners, which may be important since the issue of differing male partners in previous and current pregnancies could potentially contribute to differing outcomes by virtue of male partner chromosomal translocation or sperm DNA fragmentation.

At pre-metformin baseline, after an overnight fast, blood was obtained for measurements of fasting serum insulin and glucose, the 4G/5G polymorphism of the PAI-1 gene, PAI-Fx, and serum sex hormones, using previously reported methods (Velazquez *et al*., 1997; Balasa *et al*., 1999; Glueck *et al*., 1999a,b, 2000, 2001a,b,c). The HOMA model for insulin resistance and beta cell function was used (Haffner *et al*., 1996). Before conception, while receiving metformin 1.5–2.55 g/day, the women with PCOS were evaluated every 2 months with serial measurements of fasting serum insulin, PAI-Fx, and serum sex hormones.

After conception, patients made one follow-up visit per month throughout pregnancy with measurement of fasting serum insulin, glucose, estradiol, and progesterone. All women took prenatal vitamins with 1 mg folic acid/day.

Screening for gestational diabetes was done in conjunction with the patients' obstetricians between weeks 26 and 28 of gestation as previously described (Glueck *et al*., 2002).

At birth, all neonates were examined by paediatricians who had no knowledge of the metformin dose or duration; height and weight were recorded. At 'well-baby visits' at 3 and 6 months of life, paediatricians obtained infants' heights and weights and reviewed motor and social development. Parents and paediatricians were asked to report any apparent abnormalities in accretion of height or weight and in motor and/or social development to us. The American Academy of Paediatrics motor and social development questionnaire (1993) was completed by the infants' parents and reviewed in detail with the paediatricians and with a principal investigator (C.J.G.). At months 3 and 6, the Academy's questionnaire included five questions. Each question was given a numerical score of 1, and entirely normal motor and social development had a score of 100%.

Outcome measures

Outcome measures included development of gestational diabetes, number of first trimester SAB, live births, normal ongoing pregnancies ⩾13 weeks, nature of intrauterine fetal development by sonography, congenital defects, infant birthweight and height, and height, weight, and motor and social development during the first 6 months of life.

Neonatal weight and height

Gender-specific percentiles for height and weight at birth in the 53 neonates with gestation ⩾37 weeks [84% of 63 live births to date (Figure 1)] were assigned using year 2000 CDC growth charts for the United States (National Center for Health Statistics). Gender-gestational age-specific percentiles for birth height and weight in the 10 neonates born before 37 weeks gestation were supplied (Lubschenco *et al*., 1996). At months 3 and 6, gender-specific percentiles for height and weight were assigned using year 2000 CDC growth charts for the United States (National Center for Health Statistics).

Statistical analysis

McNemar's test for paired data (SAS/STAT, 1997) was used to compare outcomes in 40 women's 46 current pregnancies, (47 fetuses;

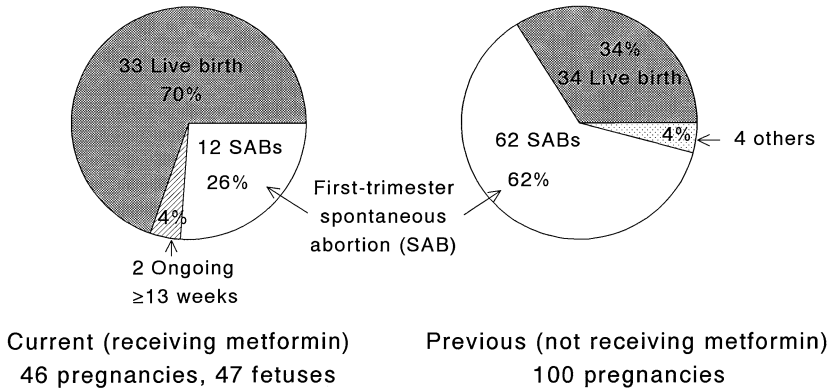

Figure 2. Current (on metformin) and previous (no metformin) pregnancy outcomes in 40 women with polycystic ovarian syndrome. Without metformin the 40 women had 100 pregnancies with 34 (34%) live births and 62 (62%) first trimester spontaneous abortions (SAB). On metformin, the 40 women had 46 pregnancies, 47 fetuses (one twin pregnancy, six women with two singleton pregnancies, 33 women with one singleton pregnancy). Metformin reduced first trimester SAB from 62 to 26% (McNemar's $S = 32$, df = 1; $P < 0.0001$).

one twin pregnancy, six women with two singleton pregnancies, 33 women with one singleton pregnancy) on metformin paired with 100 previous pregnancies without metformin in the same 40 women (Figure 2). χ^2-Analyses (SAS/STAT, 1997) were used to compare pregnancy outcomes, to compare pregnancy outcomes when metformin was continued versus those when it was stopped at the end of the first trimester, and to compare percentile distributions of infant height and weight at birth, 3 and 6 months of age with normal CDC growth charts.

Comparisons of fasting serum insulin, HOMA insulin resistance, weight, and body mass index (BMI), pre-metformin at study entry versus last pre-pregnancy visit on metformin, were made by paired Wilcoxon tests (SAS/STAT, 1997).

In the full cohort of 72 women, stepwise logistic regression (SAS/STAT, 1997) was carried out with the total number of first trimester SAB (0, 1–2, ⩾3) in previous and current pregnancies as the dependent variable, and pre-metformin, entry maternal fasting serum insulin, PAI-1 genotype, PAI-Fx, age, and BMI as explanatory variables.

A conditional logistic regression model was run in the 72 women with current pregnancy outcomes as dependent variables (first trimester SAB, live births and normal ongoing pregnancies ⩾13 weeks gestation) and maternal age and change in insulin, PAI-Fx, and weight on metformin from study entry to conception as explanatory variables.

A separate stepwise logistic regression model was run in the 72 women with current pregnancy outcomes as dependent variables and explanatory variables including maternal age, weight, insulin, previous pregnancy outcomes, type of conception (spontaneous, other), and lovenox use (17 fetuses) during pregnancy.

Power and sample size calculations were carried out (Sokol and Rohlf, 1995), based on the results of the current study. These calculations identified how many cases and controls would be needed for a placebo-controlled, blinded study of metformin's effects on first trimester SAB, to allow declaration of a difference, at a significance level alpha = 0.05, between cases' and controls' pregnancy outcomes, with a power of 80 or 90%.

Results

Entry, pre-metformin characteristics of the patients

Of the 72 women, 39 (54%) were amenorrhoeic, and 33 (46%) were oligomenorrhoeic; 11 women had 1–3 menses/year, 15 had 4–6, seven had 7–9. In addition to their oligoamenorrhoea, all 72 women had documented clinical and/or biochemical hyperandrogenism.

The cohort was obese, with median BMI 33.0 kg/m^2, (interquartile range 29.0–38.8) and median weight 91.6 kg, (interquartile range 75.5–116.4); 63% of the women had BMI greater than or equal to the Lipid Research Clinics (LRC) 95th percentile for age-matched women in a general population (Lipid Research Clinics, 1980). The women were taller than age-matched women from the LRC study, with 24% of women with PCOS in the LRC upper decile ($P < 0.0001$). Median fasting serum insulin was 18 μIU/ml (interquartile range 12–28); 53% of the women had fasting hyperinsulinaemia (insulin >17 μIU/ml) and 32% had insulin resistance by the HOMA method.

Pregnancy outcomes

Of the 72 women on metformin, 58 (81%) conceived spontaneously, two with artificial insemination (3%), 10 (14%) with 50 mg Clomid, one (1%) with Pergonal, and one (1%) by IVF. Of 66 fetuses conceived spontaneously and/or by artificial insemination, there were 11 first trimester SAB (16.7%), the same as 16.7% (3/18 fetuses) conceived on metformin and Clomid, Pergonal, or IVF. In a logistic regression model, with dependent variables being current pregnancy outcome and explanatory variables including maternal age, weight, insulin, previous pregnancy outcomes, type of conception (spontaneous, other) and Lovenox use (17 fetuses) during pregnancy, there were no significant explanatory variables. Aspirin was not used. Pregnancy outcomes could be pooled without adjustment for type of conception or Lovenox.

In the total cohort of 72 women (81 pregnancies, 84 fetuses), to date there have been 63 normal live births without congenital defects (75%), 14 first trimester SAB (17%), and seven ongoing pregnancies ⩾13 weeks with normal sonograms without congenital defects (8%) (Figure 1). Rates of first trimester SAB did not differ (17 versus 14%) in the 70 fetuses where metformin was continued through pregnancy, and in 14 where it was stopped (at a median of 12 weeks gestation).

From a total of 37 fetuses in 32 women on metformin without a previous pregnancy, there were two SAB (5.4%), 30 live births (81%) and five ongoing pregnancies ⩾13 weeks (14%). This group had a lower SAB rate than the other two groups below (Fisher's $P = 0.046, 0.057$). From a total of 37 fetuses in 30 women on metformin with ⩾1 pre-metformin SAB, there were nine SAB (24%), 26 live births (70%) and two ongoing pregnancies ⩾13 weeks (5%). From 10 fetuses in 10 women on metformin with ⩾1 pre-metformin live birth without SAB, there were three SAB (30%) and seven live births (70%).

Previously, without metformin, 40/72 women had 100 previous pregnancies (100 fetuses) with 34 (34%) live births and 62 (62%) first trimester SAB (Figure 2). In current pregnancies on metformin in these 40 women (46 pregnancies, 47 fetuses), there have been 33 live births (70%), two pregnancies ongoing ⩾13 weeks (4%), and 12 SAB (26%) (McNemar $S = 32$, df $= 1$, $P < 0.0001$) (Figure 2).

Infants' height and weight at birth, 3 and 6 months follow-up, motor and social development at 3 and 6 months follow-up

In the 63 live births, neither weight nor height differed from the normal neonatal population. Of the 63 live births, 62 are now >3 months old and 54 are >6 months old. Data for height and weight at 3 and 6 month follow-up were available for 49 of the 62 infants (79%) at 3 months and for 44 of the 54 (81%) at 6 months. At 3 months, the distribution of height was skewed to both the bottom and top deciles versus 'CDC normal' 3 month old infants ($P = 0.0005$), and weight did not differ ($P = 0.09$). At 6 months, the distribution of height was skewed to the top decile versus 'CDC normal' 6 month old infants ($P = 0.008$), and weight did not differ.

The women with PCOS were taller than the age-matched LRC women ($P < 0.0001$). In the PCOS kindreds, neonates' heights at birth and infants' heights at age 6 months were correlated with maternal height ($r = 0.25$, $P = 0.046$; $r = 0.36$, $P = 0.019$ respectively).

Mean ± SD motor-social development scores at 3 ($n = 51$) and 6 months ($n = 47$) were respectively 95 ± 11 (out of 100 maximum) and 98 ± 6. The infants' paediatricians reported no cases of significant retardation in motor–social development.

Metformin effects on insulin, HOMA insulin resistance, BMI and PAI-Fx

In 50 women, paired baseline and last pre-pregnancy visit data were available for insulin, HOMA insulin resistance, weight, BMI, and PAI-Fx. Median, pre-metformin, entry insulin (23 μIU/ml) fell after metformin treatment to 12 μIU/ml at the last pre-pregnancy visit ($P < 0.0001$). Median, pre-metformin, entry HOMA insulin resistance fell from 4.73 at entry to 2.55 on metformin ($P < 0.0001$). Median, pre-metformin, entry weight fell on metformin from 93.6 to 86.8 kg at the last pre-pregnancy visit ($P < 0.0001$), and BMI fell from 33.7 to 30.7 kg/m^2 ($P < 0.0001$). Median, pre-metformin entry PAI-Fx (15.3 IU/ml) was higher than the last pre-pregnancy level on metformin (10.1) ($P = 0.0019$).

Development of gestational diabetes

In 68 pregnancies on metformin [63 live births (Figure 1), five ongoing pregnancies ⩾26 weeks], gestational diabetes developed in three pregnancies (4%). These three women all had gestational diabetes in previous pregnancies without metformin. Gestational diabetes was diagnosed in 9/34 (26%) previous pregnancies not on metformin. In paired comparisons of previous live birth pregnancies without metformin and current live birth or ⩾26 weeks gestation pregnancies on metformin in the same 40 women (Figure 2), there was a reduction in development of gestational diabetes (McNemar's $S = 5$, $P = 0.025$).

Correlates of first trimester spontaneous abortion

With the total number of first trimester SAB in the 72 womens' previous and current pregnacies as the dependent variable, and entry (pre-conception) maternal fasting serum insulin, PAI-1 genotype, PAI-Fx, age, and BMI as explanatory variables, by stepwise logistic regression, entry fasting serum insulin was a significant independent explanatory variable for total (previous and current) first trimester SAB, odds ratio 1.32 for each 5 μIU/ml increment in insulin, 95% confidence intervals 1.09–1.60 ($P = 0.005$).

By conditional logistic regression, pregnancy outcomes on metformin were not significantly correlated with metformin-induced change in insulin, weight, or PAI-Fx from study entry to last pre-conception measurement.

Safety

There was no maternal lactic acidosis or maternal hypoglycaemia. There have been no major birth defects in the 63 live births as determined by paediatricians without knowledge of metformin dose or duration, and there have been no congenital defects or evidence of intrauterine growth retardation by sonography in the seven fetuses ⩾13 weeks. Seventy of the 84 fetuses (83%) have had a favourable outcome to date (Figure 1). There have been no second or third trimester fetal losses.

No cases of neonatal hypoglycaemia requiring intervention occurred.

Gestation was ⩾37 weeks in 53 infants (84% of live births), with median gestation duration 39 weeks (interquartile range 38, 40). Gestation was <37 weeks in 10 infants (16% of live births), with a median gestation duration of 34 weeks (interquartile range 26–35).

Power and sample size estimates

To determine whether the miscarriage rate on metformin was less than in previous pregnancies without metformin at the 5% significance level, the current study's sample size had a power >87%. Based on current study results, to perform a successful randomized controlled clinical trial at a significance level of 5% with a power of 80%, 34 pregnancies would be needed for each treatment group (metformin, placebo), and for a power of 90%, 44 pregnancies in each group.

Based on current study results, to detect a reduction of SAB by 30, 40, 50 and 60%, at the 5% significance level in a

randomized, controlled trial, with a power of 90%, 154, 90, 59 and 41 pregnancies would be needed for each treatment group respectively (metformin, placebo).

Discussion

Congruent with our pilot study (Glueck *et al*., 2001b), with our study of gestational diabetes (Glueck *et al*., 2002), and with a recent report (Jakubowicz *et al*., 2002), metformin therapy in women with PCOS during pregnancy was safely associated with a significant reduction in early pregnancy loss. Moreover, similar to our previous studies (Glueck *et al*., 2001b, 2002), and those of Jakubowicz *et al*. (2002), the salutary reduction in pregnancy loss in the current study was striking in women who had never previously conceived, as well as in women with both previous SAB or previous successful live births without metformin. Consistent with our previous studies (Glueck *et al*., 2001b, 2002), and with the report of Jakubowicz *et al*. (2002), metformin was not associated with any adverse fetal outcomes or congenital abnormalities as determined by paediatricians with no knowledge of the metformin treatment schedule. Moreover, there were no neonates identified by their paediatricians or obstetricians as exhibiting intrauterine growth retardation. Accretion of height and weight in the first 6 months of life was comparable to the general United States paediatric population (CDC growth charts 2000), and motor and social development were normal. The paediatrician-confirmed absence of congenital abnormalities, accompanied by normal routine 3 and 6 month well-baby examinations by the same paediatricians, and normal motor and social development over time, all testify to the safety of the metformin treatment programme during pregnancy. We will continue surveillance of accretion of height and weight and motor–social development up to 5 years of age, and for as long as feasible after age 5 years.

The current report can be viewed as an observational study on metformin, where, to date, of 84 fetuses conceived by 72 women, there have been 63 live births (75%), seven ongoing pregnancies $\geqslant$13 weeks (8%), and 14 first trimester SAB (17%). In the past, without metformin, 40 of these 72 women had much less favourable pregnancy outcomes in 100 fetuses, with 34 live births (34%) and 62 first trimester SAB (62%). Results similar to those of the current study have been reported in a recent retrospective observational study of PCOS (Jakubowicz *et al*., 2002). Of 31 women (31 pregnancies) without metformin, the early pregnancy loss rate was 41.9%, while in 65 women (68 pregnancies) on metformin, the early pregnancy loss rate was 8.8%.

The current report can also be assessed by comparing antecedent pregnancies that occurred in the absence of metformin and the current pregnancies on metformin in the same women. We speculate that by using each patient as her own control, the multiple variables which could affect pregnancy outcome may be considerably obviated because they intrinsically should be more comparable in the same woman than among different women. We recognize that low carbohydrate–high protein diets and more careful follow-up of the current pregnancies versus previous pregnancies in the same woman might potentially inflate the success of the current study. Comparing 100 fetuses without metformin in 40 women versus 47 fetuses (46 pregnancies) on metformin, first trimester SAB on metformin was 26% (12/47) and 62% (62/100) without metformin ($P < 0.0001$); at the 5% significance level, the sample size of the current study had a power >87%. Pregnancy outcomes did not differ in women who stopped metformin at the end of the first trimester versus those who continued it throughout. Whether metformin's beneficial effects on pregnancy outcome are primarily realized during the first trimester needs to be examined in a placebo-controlled trial of women with PCOS who conceive on metformin, continue it through the first trimester, and then are randomized to metformin or placebo for the remainder of the pregnancy. However, a major benefit of continuing metformin beyond the first trimester and throughout pregnancy in women with PCOS is a sharp reduction in gestational diabetes, from 26% (previous pregnancies without metformin) to 4% (on metformin) in the current study, and from 31 to 3% as reported previously (Glueck *et al*., 2002). Moreover, on metformin, the prevalence of gestational diabetes (4%) approximated that in the general population (Engelgau *et al*., 1995).

A randomized, placebo-controlled, double-blind, controlled clinical trial will be required to optimally confirm the SAB-sparing capability of metformin revealed in the current and previous observational, non-blinded studies (Glueck *et al*., 2001b, 2002; Jakubowicz *et al*., 2002). A third arm of a controlled clinical trial might include women without any preconception or within-pregnancy metformin who conceived with Clomid or Pergonal, and a fourth arm, those who conceived with IVF. Without stratification (as below), based on our current study, at a significance level = 0.05, and with a power of 80%, 34 cases and 34 controls would be needed for a randomized, placebo-controlled trial. Based on the current study, to detect reduction in SAB by 30, 40, 50 and 60%, at the 5% significance level in a randomized controlled trial, with a power of 90%, 154, 90, 59 and 41 pregnancies respectively would be needed for each treatment group (metformin, placebo). However, a controlled trial would probably require an even larger sample size to allow stratification at entry for variables which could affect pregnancy outcomes: maternal age, number and outcome of previous pregnancies, socioeconomic status, race, habitual diet, exercise, alcohol, and smoking habits, weight, previous gestational diabetes, spontaneous conception versus assisted conception (embryo transfer, etc.), type 2 diabetes, fasting serum insulin, PAI-Fx, and thrombophilic and hypofibrinolytic risk factors for major complications of pregnancy (Glueck *et al*., 1999a, 2000, 2001a).

Of paramount importance, in the current study, reduction in the rate of first trimester SAB from 62 to 26% was achieved without evident teratogenicity, without intrauterine growth retardation, without maternal or neonatal side-effects, without adverse effects on birthweight and height, and without adverse effects on accretion of height or weight, or on motor or social development at 3 and 6 months of age. The skewing of infants'

heights towards higher percentiles at 6 month follow-up may, speculatively, reflect an association with their mothers' height (Ounsted *et al*., 1982), which was greater than the age-matched LRC female population. Maternal height correlated with infants' height at 6 month follow-up ($r = 0.25$, $P = 0.046$). The apparent absence of teratogenicity in the current study is encouraging but not surprising, given the lack of teratogenicity observed with metformin in our pilot study of 19 women with PCOS (Glueck *et al*., 2001b), in our study of gestational diabetes (Glueck *et al*., 2002), in the study by Jakubowicz *et al*. (2002) of 65 women with PCOS, and in previous reports (Coetzee and Jackson, 1979, 1980, 1984, 1985–6; Jackson and Coetzee, 1979). Moreover, in whole embryo culture, metformin produces no alterations in embryonic growth and no major malformations (Denno and Sadler, 1994). Despite the encouraging findings of the current study (63 normal live births and seven pregnancies ⩾13 weeks to date with normal sonograms without evident congenital defects; Figure 1), and despite the congruence of our findings with those of Jakubowicz *et al*. (2002), a larger number of live births in a double-blind, placebo-controlled trial would add weight to the current evidence against teratogenicity.

Increased perinatal mortality in women with pre-pregnancy type 2 diabetes mellitus treated with metformin versus those treated with sulphonylurea and a reference group treated with insulin has been reported (Hellmuth *et al*., 2000). Our cohort was very different from that of Hellmuth *et al*., having PCOS, with exclusion of women having pre-conception type 2 diabetes mellitus. However, our limited, preliminary experience in pregnancy outcomes following metformin therapy throughout pregnancy in five women with pre-conception type 2 diabetes has been favourable. In these five women, of 10 fetuses in previous pregnancies without metformin, there were two live births (20%) versus five live births of six fetuses (83%) on metformin (Goldenberg *et al*., 2002).

The high rate of first trimester SAB in women with PCOS without metformin is not surprising (Glueck *et al*., 1999a, 2000, 2001a; Jakubowicz *et al*., 2002). Since metformin has beneficial effects on multiple risk factors for SAB (hyperinsulinaemia, insulin resistance, hyperandrogenaemia, obesity, PAI-Fx), decreasing hyperinsulinaemic insulin resistance should lower SAB (Glueck *et al*., 2001b, 2002; Jakubowicz *et al*., 2002). Glueck *et al*. (2001b) have previously postulated that metformin's reduction in PAI-Fx contributes to a reduction in SAB in women with PCOS. Gris *et al*. identified high PAI-Fx as one of the most frequent haemostasis-related abnormalities in 500 consecutive women with unexplained primary recurrent miscarriages (Gris *et al*., 1997). In the current study, among maternal fasting serum insulin, PAI-1 genotype, PAI-Fx, age, and BMI as explanatory variables, fasting serum insulin was a significant independent explanatory variable for first trimester SAB, congruent with the study by Fedorcsak *et al*. (2000). Metformin's protective effects against first trimester SAB appear to accounted for, in part, by its insulin-lowering effect, as in the current study.

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