Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin

Charles J. Glueck1, Ping Wang, Naila Goldenberg and Luann Sieve-Smith

Cholesterol Center, Jewish Hospital, ABC Building, 3200 Burnet Avenue, Cincinnati, OH 45229, USA

1To whom correspondence should be addressed. E-mail: gluekch@healthall.com

BACKGROUND: We sought to determine whether metformin, which had facilitated conception in 72 oligoamenorrheic 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 oligoamenorrhea, 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)
hormones, using previously reported methods (Velazquez et al., 1996). At pre-metformin baseline, after an overnight fast, blood was obtained for measurements of fasting serum insulin and 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 (Lubscheno 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;
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). $\chi^2$-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 Rohlff, 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/m², (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 months 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/m² ($P < 0.0001$). 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 women’s previous and current pregnancies 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 ≥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 antecedent pregnancies that occurred in the absence of metformin, while in 65 women (68 pregnancies) on metformin, the early pregnancy loss rate was 8.8%.

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 (hyperinsulinemia, insulin resistance, hyperandrogenemia, obesity, PAI-Fx), decreasing hyperinsulinemia 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.

References


PCOS, metformin and pregnancy

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