Height, weight, and motor–social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy

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BACKGROUND: We prospectively assessed growth and motor–social development during the first 18 months of life in 126 live births (122 pregnancies) to 109 women with polycystic ovary syndrome (PCOS) who conceived on and continued metformin (1.5–2.55 g/day) through pregnancy. METHODS: The lengths and weights of PCOS neonates were compared with gender-specific Centers for Disease Control and Prevention (CDC) infant data. Gestational diabetes (GD) and pre-eclampsia in women with PCOS were compared with 252 healthy women without PCOS who had ≥1 live birth (262 live births). RESULTS: There were 101 out of 126 (80%) term (≥37 gestational weeks) PCOS births, which was not significantly different (P = 0.7) from controls, 206 out of 252 (81.7%). There were two (1.6%) birth defects. GD occurred in nine out of 119 PCOS pregnancies (7.6%) versus 40 out of 251 (15.9%) controls, P = 0.027. The prevalence of pre-eclampsia did not differ in PCOS versus control pregnancies (4.1 versus 3.6%, P = 0.8). The birth length and weight of the 52 male neonates did not differ (P > 0.05) from those of CDC males; the 74 female neonates were shorter than CDC females (48.9 ± 66 5.4 versus 50.6 ± 66 2.7 cm, P = 0.006) and weighed less (3.09 ± 66 0.85 versus 3.29 ± 66 0.52 kg, P = 0.04). There were no systematic differences in growth between PCOS and CDC infants over 18 months. At 3, 6, 9, 12 and 18 months, of a potential 100% motor–social development score, scores (±SD) were 95 ± 13, 98 ± 8%, 95 ± 10, 97 ± 8 and 94 ± 16%; no infants had motor–social developmental delays. CONCLUSIONS: Metformin reduced development of GD, was not teratogenic and did not adversely affect birth length and weight, growth or motor–social development in the first 18 months of life.

Key words: gestational diabetes/infant development in the first 18 months of life/metformin/pre-eclampsia/polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is characterized by oligo-amenorrhea, clinical and/or biochemical hyperandrogenism, polycystic ovaries, infertility and, commonly, insulin resistance, hyperinsulinaemia, morbid obesity and type 2 diabetes (Kawadzki and Dunaif, 1992; Velazquez et al., 1994, 1997a,b; Glueck et al., 1999b, 2001b,c, 2002a,b,c, 2004a,b; Moghetti et al., 2000; ESHRE/ASRM, 2004). The insulin-sensitizing drug metformin (1.5–2.55 g/day) ameliorates the endocrinopathy of PCOS by reducing hyperinsulinaemia-mediated hyperandrogenism, facilitating resumption of predominantly ovulatory normal menses in 55 (Moghetti et al., 2000) to 91% of adult women (Glueck et al., 1999b) and in 91% of teenage girls (Glueck et al., 2001c). Without metformin, spontaneous abortion (SAB) is common in women with PCOS, occurring in 73 (Glueck et al., 2001b), 62 (Glueck et al., 2002c), 44 (Glueck et al. 1999a), 42 (Jakubowicz et al., 2002), 39 (Glueck et al., 2001b) and 25% of pregnancies (Wang et al., 2001).

Metformin has beneficial effects on risk factors for the high rate of first trimester SAB in PCOS [hyperinsulinaemia, insulin resistance, hyperandrogenaemia, obesity and hypofibrinolytic high levels of plasminogen activator inhibitor activity (PAI-Fx)] (Glueck et al., 1999a, 2001a, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002). Within this frame of reference, metformin lowers the rate of first-trimester SAB (Glueck et al., 2001b, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002).

Metformin does not appear to be teratogenic whether given to women with type 2 diabetes, gestational diabetes (GD) or PCOS (Coetzee and Jackson, 1979, 1980, 1984, 1985; Jackson and Coetzee, 1979; Glueck et al., 1999b, 2001a, 2002a,b,c, 2004a,b; Heard et al., 2002; Jakubowicz et al., 2002).

Beyond reduction in SAB (Glueck et al., 2002c), reduction in pre-eclampsia (Glueck et al., 2004a) and reduction in macrosomia (Glueck et al., 2004a), another reason for continuing metformin during pregnancy in women with PCOS is its reduction in GD and its positive effects on the
mechanisms of GD (Glueck et al., 2002a,c, 2004a,b). In a previous study of 95 live births, development of GD in women with PCOS on metformin during pregnancy did not differ from controls [nine out of 95 pregnancies (9.5%) versus 40 out of 251 (15.9%), \( P = 0.12 \)], (Glueck et al., 2004a). By reducing pre-conception weight, insulin, insulin resistance and insulin secretion, and by reducing the physiological hyperinsulinaemia of pregnancy, metformin helps to prevent development of GD and improves pregnancy outcomes in women with PCOS (Glueck et al., 2004b).

Our previous studies suggested that metformin during pregnancy in women with PCOS does not adversely affect their neonates’ birth weight or length, or growth in the first 6 months of life (Glueck et al., 2002c). In 63 live births to women with PCOS who took metformin through pregnancy, birth weight (\( P = 0.19 \)) and height (\( P = 0.14 \)) did not differ from those of normal neonatal populations (Glueck et al., 2002c). At 6 month follow-up, height was greater than (\( P = 0.008 \)) and weight did not differ from (\( P = 0.26 \)) those of normal infant populations; motor–social development was normal (Glueck et al., 2002c).

Given the increasing evidence for the value of continuing metformin throughout pregnancy in women with PCOS, in the current study, our specific aim was to assess prospectively birth length and weight, growth and motor–social development during the first 18 months of life in 126 live births (122 pregnancies) to 109 Midwestern USA women with PCOS who conceived on and continued metformin through pregnancy.

### Materials and methods

We used a protocol approved by the Jewish Hospital Institutional Review Board. All patients gave signed informed consent. Procedures followed were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki. The diagnosis of PCOS was made using revised 2003 ESHRE/ASRM consensus conference criteria (ESHRE/ASRM, 2004) (two out of three): (i) oligomenorrhea or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; and (iii) polycystic ovaries (see also Table I).

### Table I Diagnostic characteristics of the 109 PCOS patients at pre-conception, pre-treatment study entry

<table>
<thead>
<tr>
<th>No. of menses in previous year</th>
<th>0</th>
<th>1–3</th>
<th>4–6</th>
<th>7–10</th>
<th>11–12</th>
<th>All n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 52 (48%)</td>
<td>45 (87%)</td>
<td>22 (88%)</td>
<td>18 (95%)</td>
<td>9 (82%)</td>
<td>1 (50%)</td>
<td>95 (87%)</td>
</tr>
<tr>
<td>n = 25 (23%)</td>
<td>32 (62%)</td>
<td>13 (52%)</td>
<td>6 (32%)</td>
<td>10 (91%)</td>
<td>2 (100%)</td>
<td>66 (58%)</td>
</tr>
<tr>
<td>n = 19 (17%)</td>
<td>51 (98%)</td>
<td>24 (96%)</td>
<td>19 (100%)</td>
<td>11 (100%)</td>
<td>2 (100%)</td>
<td>107 (98%)</td>
</tr>
<tr>
<td>n = 11 (10%)</td>
<td>16 (31%)</td>
<td>3 (12%)</td>
<td>1 (5%)</td>
<td>5 (45%)</td>
<td>1 (50%)</td>
<td>32 (30%)</td>
</tr>
<tr>
<td>n = 2 (2%)</td>
<td>6 (12%)</td>
<td>5 (20%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>11 (10%)</td>
</tr>
</tbody>
</table>

### Exclusion of other aetiologies

Exclusionary criteria included serum creatinine >1.5 mg/dl, type 1 diabetes mellitus (DM), type 2 DM on pharmacological therapy, pituitary insufficiency, persistent hyperprolactinaemia and congenital adrenal hyperplasia (Kawadzki and Dunaif, 1992; Glueck et al. 1999b, 2001b, 2002c).

We used the definitions of Laven et al. (2002) for oligomenorrhea (bleeding intervals between 35 days and 6 months), or amenorrhoea, bleeding interval >6 months (Table I).

Since 100% of our prospectively studied patients with PCOS conceived on metformin, we did not have access to infants born to a second, potentially informative control group, i.e. women with PCOS who conceived without metformin and, while following the same protein-enriched, carbohydrate-restricted diet, did not take metformin during pregnancy. We also did not have access to infants born to a prospectively studied control group of normal pregnant women, matched to those with PCOS by age, parity and pre-conception body mass index (BMI), followed longitudinally on the same high-protein, low-carbohydrate diet throughout pregnancy.

### Women with PCOS

Non-pregnant women were referred to our centre for diagnosis of PCOS and for study of the efficacy and safety of metformin (Glueck et al., 1999b), or metformin and pioglitazone (Glueck et al., 2003). None of the women, having been offered participation in the metformin treatment study declined participation. The current prospective, open label, single centre, consecutive case series study included 109 women (age 31 ± 5 years, 104 Caucasian, five other) from the Midwestern USA who conceived on metformin, 1.5–2.55 g/day, and had \( \geq 1 \) live birth. The 109 women were enrolled consecutively in the pregnancy follow-up study after they had conceived, and were followed prospectively in Cincinnati or in their hometowns, under our direction, and using our protocol (Glueck et al., 2001b, 2002c, 2004a,b). Women were included consecutively in the current study irrespective of outcome(s) of their previous pregnancies without metformin, to avoid selection bias based on previous pregnancy outcomes. All pregnancies (historical and current) were conceived with the same partners, which may be important since the issue of differing male partners in previous and current pregnancies potentially could 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., 1994, 1997a,b; Glueck et al., 1999a,b, 2000, 2001a,b,c). HOMA insulin resistance and insulin secretion were calculated as per Haffner et al. (1996). Normal limits for pre-conception, pre-treatment systolic and diastolic blood pressure, high-density lipoprotein (HDL) cholesterol and triglycerides were taken from the recent Adult Treatment Panel III guidelines (National Institutes of Health, 2001).

Pre-conception, PCOS women with BMI <25 kg/m² or ≥25 were instructed, respectively, in a 2000 or 1500 calories/day, high-protein (26% of calories), low-carbohydrate (44%) diet (42% of carbohydrate was complex), with 30% of the calories as fat and a polyunsaturated/saturated ratio of 2:1 (Glueck et al., 2002c). After conception, calorie restrictions were dropped, but continued adherence to the low-carbohydrate, high-protein diet was encouraged. At least 1 month before and throughout pregnancy, folic acid (1 mg/day) was given to reduce the likelihood of neonatal spina bifida (American Academy of Pediatrics, 1999).

Pre-conception, metformin was started at 1.5 g/day, with the dose increased over 2–4 months to a target of 2.55 g/day (850 mg with each meal). Although the targeted metformin dose (2.55 g/day) was taken in 74 of 122 pregnancies (61%), in some women we had to reduce metformin to the highest dose level tolerated, 1 g/day in five of 122 pregnancies (4.1%), and 1.5–2 g/day in 43 of 122 pregnancies (35%). While receiving metformin, the women with PCOS were evaluated every 2 months with serial measurements of fasting serum insulin, PAI-Fx and serum sex hormones. After conception, we recommended that metformin be continued throughout pregnancy, and continued without change in dose, but it could be stopped by the concurrent request of both the patient and her obstetrician.

During pregnancy, women with PCOS made monthly follow-up visits to our centre with measurement of weight, and, after an overnight fast, serum insulin, glucose, testosterone, estradiol, progesterone and PAI-Fx (Glueck et al. 2002c, 2004a,b). At each monthly visit during pregnancy, after a 5 min resting period, seated blood pressure was obtained by a single observer and recorded; diet was reviewed, as was adherence to metformin and metformin dose. All medical aspects of the patients’ pregnancies were managed directly by the investigators.

At gestation weeks 26–28, in collaboration with the patients’ obstetricians, evaluation for GD was done (O’Sullivan et al., 1973; American Diabetes Association, 1986).

Pre-eclampsia was diagnosed by the ISSHP criteria (Brown et al., 2001) which include blood pressure >140/90 mmHg on two separate occasions 4 h apart or a single diastolic pressure ≥110 mmHg, in association with ≥2+ proteinuria by dipstick testing, in the absence of renal disease or infection.

At birth, all neonates were examined by paediatricians who had no knowledge of the metformin dose or duration; height and weight were recorded, along with any birth defects. At well-baby visits at 3, 6, 9, 12 and 18 months of life, paediatricians obtained infants’ heights and weights, reviewed motor and social development, and documented any birth defects which became evident during the first 18 months of life. 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 Pediatrics 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, 6, 9, 12 and 18, the Academy’s questionnaire included five, five, seven and six questions, respectively. Each question was given an equivalent score of 1, and entirely normal motor and social development had a score of 100%.

Community controls
The 109 women with PCOS were compared with 252 prospectively followed healthy women (age 29 ± 6 years, 226 Caucasian, 25 African-American, one other) not known to have PCOS (Glueck et al., 2004a). These 252 women consecutively delivered 262 live births, 242 singleton and 10 sets of twins, in a suburban–urban community practice of obstetrics (Glueck et al., 2004a). Although the controls from the community obstetrics practice had regular menses, had no clinical signs of hyperandrogenism and had not been diagnosed by their obstetricians as having PCOS, they did not have serological tests to rule out hyperandrogenism.

Outcome measures
Outcome measures included major birth defects, infant birth weight and height, and growth and motor–social development during the first 18 months of life. Additional outcome measures included maternal GD and pre-eclampsia.

Statistical analysis
Infants’ height and weight by gender at birth, 3, 6, 9, 12 and 18 months of age were compared with gender-specific Centers for Disease Control and Prevention (CDC) data for US male and female infants (Kuczumarski et al., 2002) using t-tests (SAS/STAT, 2002). Comparisons of women with PCOS who conceived on metformin versus community controls were made using χ² tests or Fisher’s exact tests for categorical variables, and Wilcoxon non-parametric tests for numerical variables (SAS/STAT, 2002).

Results

Universe of PCOS patients
Over a 7 year time period (April 30, 1996 to March 24, 2003), among 886 women (age ≥16, <47 years) referred for diagnosis of PCOS and for study of efficacy and safety of metformin or metformin plus pioglitazone in PCOS (Glueck et al., 1999b, 2003), 126 women (ages 21.0–46.8 years) subsequently became pregnant while taking metformin (1.5–2.55 g/day). One woman conceived on combined metformin (2.55 g/ day) + pioglitazone (45 mg/day). Pioglitazone was immediately stopped, and metformin continued throughout the pregnancy.

At the time of this report, these 127 women had 151 pregnancies (156 fetuses). At the time of this report, of the 156 fetuses, there were 126 live births (122 pregnancies), nine ongoing pregnancies (>13 weeks gestation) and 21 first-trimester SABs (13%).

During the 7 year time period, among the 886 women with PCOS, 759 other women with PCOS started participation in the metformin–diet programme and did not conceive. Of these 759 women, 310 were single, 368 were married, nine had previous hysterectomy, and 197 used contraceptive methods (barrier, intrauterine device or tubal ligation) and did not wish to become pregnant. Besides the 127 women who conceived, there were 282 women (of 759) who wished to conceive but have not conceived to date.

The 127 women who conceived were relatively thinner than the 282 women who have, to date, failed to conceive (BMI 33.7 ± 7.9 versus 37.7 ± 8.4, P < 0.0001), and younger (31 ± 5 versus 33 ± 5 years, P = 0.0003). The 127 women who
conceived did not differ \((P > 0.2)\) from the 282 women who failed to conceive in terms of pre-treatment fasting serum insulin \((21 \pm 16 \text{ versus } 26 \pm 28 \text{ uU/ml})\), HOMA insulin resistance \((5.09 \pm 5.41 \text{ versus } 6.77 \pm 11.57)\) and HOMA insulin secretion \((296 \pm 310 \text{ versus } 333 \pm 335)\).

On metformin, of the 122 pregnancies in the 109 women, 105 (86%) were conceived spontaneously, two (2%) with artificial insemination, 12 (10%) with 50 mg clomid, two (2%) with IVF and one (1%) with pergonal.

Metformin was continued throughout pregnancy in 104 of the 122 (85%) pregnancies, and discontinued in 18 pregnancies at a median of 12 weeks gestation by women’s obstetricians who did not want metformin continued beyond the first trimester. Of the 122 pregnancies (126 live births), metformin 1 g/day was taken in five pregnancies (4.1%), 1.5 g/day was taken in 34 (28%), 1.7 g/day was taken in five (4.1%), 2 g/day was taken in four (3.3%), and 2.55 g/day was taken in 74 (60.7%) pregnancies. There were no differences \((P > 0.3)\) in the number of weeks of gestation, or infants’ birth height or weight comparing the 104 pregnancies where metformin was continued throughout versus the 18 where it was stopped at (median) 12 weeks gestation.

**Characteristics of PCOS in the 109 women with PCOS and >1 live birth**

At study entry, in the cohort of 109 women, mean \(\pm \text{SD} \) weight was 92.6 \(\pm\) 22.3 kg, BMI 33.5 \(\pm\) 7.6 kg/m\(^2\). Of the 109 women, 16% had BMI <25 (normal weight), 16% were overweight (BMI 25–30), 50% were obese (BMI 30–40) and 19% had extreme obesity (BMI >40) (Flegal et al. 2002). Using ATP III cutpoints (National Institutes of Health, 2001), systolic blood pressure was high (>130 mmHg) in 27%, diastolic blood pressure high (>85 mmHg) in 19%, triglycerides high (>150 mg/dl) in 29%, HDL cholesterol low (<50 mg/dl) in 64%, and fasting serum glucose high (>110 mg/dl) in 6%. Fasting serum insulin was high (>17 uU/ml) in 50% of the 109 women.

Of the 109 women, 96 had <6 menses/year, and 11 had 7–10 menses (Table I). Of the 109 women, 95 (87%) had Ferriman–Gallwey (FG) (Ferriman and Gallwey, 1961) scores \(>7\), and 63 (58%) had severe acne. Of the 109 women, 51 (47%) had \(>1\) high androgen level (Table I). Polycystic ovaries had been demonstrated before pregnancy in 94 of the 109 women (Table I).

All 109 women (100%) met the revised 2003 diagnostic criteria for PCOS (ESHRE/ASRM, 2004), having two of the following three findings (oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries) (Table I).

**GD and pre-eclampsia**

Three (2.8%) of the 109 patients had pre-conception type 2 DM controlled by diet alone, but had normal glucose tolerance testing during pregnancy on metformin. Pre-conception type 2 DM did not differ in patients (2.8%) versus community...
controls (one out of 252, 0.4%), Fischer’s $P = 0.084$. Of the 119 pregnancies in the women with PCOS, where there was no type 2 DM pre-conception; GD was diagnosed in nine (7.6%), less than in the community controls’ pregnancies (40 out of 251, 15.9%), $\chi^2 = 4.93$, $P = 0.027$. In women with PCOS, GD did not differ in pregnancies where metformin was continued throughout (eight out of 102, 7.8%) versus those where it was stopped at a median of 12 weeks gestation (one out of 17, 5.9%), Fisher’s $P = 1$. GD was more common in the community controls than in the women with PCOS despite the controls having much lower BMI (25.6 ± 5.9 versus 33.5 ± 7.6 kg/m², $P < 0.0001$).

Pre-eclampsia occurred in five of 122 (4.1%) pregnancies in the women with PCOS, not different ($P = 0.80$) from the community controls (nine out of 252, 3.6%). Pre-eclampsia did not differ in women with PCOS who continued metformin throughout pregnancy (five out of 104, 4.8%) versus those who stopped at a median of 12 weeks gestation (none out of 18, 0%), Fisher’s $P = 1$. Pre-eclampsia occurred in two of the 53 women with PCOS who were primigravidas (3.8%), not different (Fisher’s $P = 1$) from four of 91 community control primiparous women (4.4%).

**Infants’ height and weight at birth, and at 3, 6, 9, 12 and 18 months follow-up**

Of the 126 live births, 101 (80.2%) were term ($\geq 37$ gestational weeks) and 25 were <37 weeks, not different from the community controls, where 206 of 252 births (81.7%) were term, $P = 0.71$. Of the 126 live births to the women with PCOS, there were two birth defects (1.6%) (one sacrococcygeal teratoma, one tethered spinal cord).

As displayed in Figures 1 and 2, birth weight and height in the total cohort of 52 male infants and the 42 term male infants did not differ from the CDC male infant cohort (Kuczmarski et al., 2002). At 3 months, male infants were shorter than CDC males (Figures 1 and 2). At 12 months, male infants, but not term male infants, were shorter than CDC males (Figures 1 and 2). The male PCOS infant cohort was thinner than CDC males at 3, 6 and 12 months (Figure 2). Term male infants were thinner than CDC males at 3 and 6 months of age, Figure 2.

At birth, the 74 female neonates were shorter than CDC females (48.9 ± 5.4 versus 50.6 ± 2.7 cm, $P = 0.006$) and weighed less (3.09 ± 0.85 versus 3.29 ± 0.52 kg, $P = 0.04$) (Figure 3). The 74 female infants were also shorter and thinner than CDC female infants at 3 months (Figure 3), with no subsequent differences through 18 months. Body weight and height in the 59 term female PCOS infants were virtually superimposable on those of the CDC female infants (Figure 4), with the single exception of lower weight in the PCOS term female infants at age 3 months (Figure 4).

No infants were judged by their paediatricians to have abnormal accretion of height or weight from birth through 18 months.
Infants’ motor and social development

As determined by an American Academy of Pediatrics motor-social development questionnaire (1993), at 3, 6, 9, 12 and 18 months, of a potential 100% score, mean ± SD scores were 95 ± 13, 98 ± 8, 95 ± 10, 97 ± 8 and 94 ± 6%. No infants were determined to have motor or social developmental delays by this questionnaire or by their paediatricians.

Discussion

Metformin alone (Velazquez et al., 1994, 1997a, 1997b; Morin-Papunen et al., 1998; Glueck et al., 1999b, 2001c; Pirwany et al., 1999; Moghetti et al., 2000), metformin plus pioglitazone (Glueck et al., 2003) or metformin plus clomid (Vandermolen et al., 2001; Heard et al., 2002; Kocak et al., 2002; Stadtmayer et al., 2002; George et al., 2003) will restore regular ovulatory menstrual cycles to a majority of previously infertile oligo-amenorrhoeic women with PCOS, many of whom will conceive. After conception, metformin significantly reduces the otherwise high rate of SAB which characterizes PCOS (Glueck et al., 2001b, 2002a,b,c, 2004a; Jakubowicz et al., 2002), reduces the development of GD (Glueck et al., 2002a,b,c, 2004a,b), reduces the development of pre-eclampsia (Glueck et al., 2004a) and reduces the likelihood of fetal macrosomia (Glueck et al., 2002c, 2004a).

Importantly, there is no evidence that metformin is teratogenic whether given to women with type 2 DM, GD or PCOS (Coetzee and Jackson, 1979, 1980, 1984, 1985; Jackson and Coetzee, 1979; Glueck et al., 2001b, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002). In the current study, as in the past, metformin use during pregnancy was not associated with increased development of major birth defects, with the birth defect rate of 1.6% not different from the USA national 1.9% rate reported by the CDC for 1990–1991 (James et al., 2000), or 4.2% recently reported from Australia (Hansen et al., 2002).

Although the current study was prospective, women with PCOS were not randomized to a placebo–diet versus metformin–diet group, and comparisons of the development of pre-eclampsia and GD were made against healthy pregnant women without PCOS. A larger number of live births in a double-blind, placebo-controlled trial of metformin–diet versus placebo–diet throughout pregnancy would add weight to the current evidence against teratogenicity, would allow an optimal assessment of effects of diet and diet–metformin on pre-eclampsia and GD, and would allow comparison of birth height and weight and subsequent growth in infants from metformin–diet and placebo–diet groups.

Although calories and carbohydrates were restricted before conception, after conception, calorie restrictions were dropped, but continued adherence to the low-carbohydrate, high-protein diet was encouraged. We doubt that the low-carbohydrate, but calorically unrestricted diet during pregnancy had any major effects on pre-eclampsia, development of GD or neonatal weight. Although many diet and lifestyle interventions for prevention of pre-eclampsia have been carried out, as summarized by Duley (2003) ‘Overall, there is insufficient evidence for any firm conclusion about the effects of any aspect of diet or lifestyle during pregnancy’. Although there has been no systematic prospective study of carbohydrate, but not caloric restriction during pregnancy on the subsequent development of GD, carbohydrate restriction in women with diet-controlled GD results in improved glycaemic control, less need for insulin, a decrease in the incidence of large for gestational age infants and a decrease in Caesarian deliveries for macrosomia (Major et al., 1998).

The prematurity rate of 20% in infants from PCOS mothers did not differ from community controls (18%). There was no neonatal hypoglycaemia.

In women with pre-gestational type 2 DM, Hellmuth et al. (2000) reported an increased prevalence of pre-eclampsia on metformin (32%) versus 7% on sulphonylurea, versus 10% on insulin, and also reported higher perinatal mortality (11.6% on metformin, 1.3% on sulphonylureas or insulin). Hellmuth et al. (2000) used various treatment schedules initiated over a very wide range of gestation. The retrospectively selected, 42 woman control group (Hellmuth et al., 2000) was very heterogeneous and included women whose initial treatment dates varied by as much as 32 gestational weeks. In contrast to Hellmuth et al. (2000), in our recent prospective study of metformin and pre-eclampsia (Glueck et al., 2004a), there was no increase in pre-eclampsia in primarily non-diabetic women with PCOS versus controls (5.2 versus 3.6%). Moreover, in our recent study (Glueck et al., 2004a), as had been the case in previous reports (Coetzee and Jackson, 1979, 1980, 1984, 1985; Jackson and Coetzee, 1979; Glueck et al., 2001b, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002), there was no perinatal mortality, and no fetal loss in either the second or third trimesters. Our recently reported cohort (Glueck et al., 2004a) was very different from that of Hellmuth et al. (2000), having PCOS, studied prospectively with prospective controls, and largely non-diabetic, with only 2% of women with pre-conception type 2 DM. The study of Hellmuth et al. (2000) was retrospective, and included exclusively diabetic pregnancies over a 25 year period (1966–1991). Our recently reported study of PCOS, and others (Coetzee and Jackson, 1979, 1980, 1984, 1985; Jackson and Coetzee, 1979; Glueck et al., 2001b, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002) did not reveal the adverse pregnancy outcomes (increased pre-eclampsia, increased perinatal mortality) on metformin as reported by Hellmuth et al. (2000) in type 2 diabetics.

Since, as above, metformin reduces SAB, GD, macrosomia and pre-eclampsia, it is important to examine birth weight and length, growth and motor–social development in the first few years of life in neonates born to mothers with PCOS who took metformin during pregnancy. Our previous study of 63 live births to women with PCOS who took metformin during pregnancy (Glueck et al., 2002c) revealed that neither birth weight nor height differed from those of the normal neonatal population. At 6 month follow-up, infant height was greater (P = 0.008) and weight did not differ from the normal USA infant population (Glueck et al., 2002c). The infants’ paediatricians reported no cases of growth retardation (Glueck et al., 2002c). Motor and social development were normal by an American Academy of Pediatrics (1993) development questionnaire (Glueck et al., 2002c). 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 (Glueck et al., 2002c). The infants’ paediatricians reported no cases of significant retardation in motor–social development (Glueck et al., 2002c).

In the current study, birth weight and height as well as growth over the first 18 months of life did not differ systematically from CDC normal infant cohorts (Kuczynski et al., 2002). None of the infants were judged by their paediatricians to have growth retardation. By an American Academy of Pediatrics (1993) motor and social development questionnaire, mean scores, out of a maximum of 100%, ranged from 94 to 98%; no infants were judged by their paediatricians to have abnormal motor and social development.

Since metformin facilitates conception in women with PCOS and subsequently lowers their otherwise high rate of first-trimester SAB (Glueck et al., 2001b, 2002a,b,c, 2004a,b; Jakubowicz et al., 2002), it is important, as in the current study, that, when continued through pregnancy, metformin was not teratogenic, reduced GD and pre-eclampsia, did not adversely affect birth length or weight, and had no adverse effect on growth or on motor–social development in the first 18 months of life.

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PCOS, metformin, infant growth and development


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