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Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study

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BACKGROUND: Investigation of a possible effect of metformin on androgen levels in pregnant women with polycystic ovary syndrome (PCOS). METHODS: A prospective, randomized, double-blind, placebo-controlled pilot study was conducted. Forty pregnant women with PCOS received diet and lifestyle counselling and were randomized to either metformin 850 mg twice daily or placebo. Primary outcome measures were changes in serum levels of dehydroepiandrosterone sulphate, androstenedione, testosterone, sex hormone-binding globulin, and free testosterone index. Secondary outcome measures were pregnancy complications and outcome. Two-tailed *t*-tests and χ^2-tests were used. RESULTS: Maternal androgen levels were unaffected by metformin treatment in pregnant women with PCOS. While none of the 18 women in the metformin group experienced a severe pregnancy or post-partum complication, seven of the 22 (32%) women experienced severe complications in the placebo group ($P = 0.01$). CONCLUSIONS: Metformin treatment did not reduce maternal androgen levels in pregnant women with PCOS. In the metformin-treated group we observed a reduction of severe, pregnancy and post-partum complications. Metformin treatment of pregnant PCOS women may reduce complications during pregnancy and in the post-partum period.

Key words: androgens/metformin/PCOS/pregnancy outcome

Introduction

Polycystic ovary syndrome (PCOS) is a disorder characterized by polycystic ovaries, oligomenorrhoea, and hyperandrogenism. It is the most common endocrine disorder in women of fertile age. Prevalence estimates vary between 3 and 20%, depending on the diagnostic criteria used and the population studied (Franks, 1995). A prevalence of 5–17% has been reported in Caucasian women (Asuncion *et al.*, 2000).

One major concern in PCOS is reduced fertility. The rate of first trimester pregnancy loss is also considerably increased (Homburg *et al.*, 1988; Sagle *et al.*, 1988; Regan *et al.*, 1990; Balen *et al.*, 1993; Tulppala *et al.*, 1993; Clifford *et al.*, 1994; Okon *et al.*, 1998; Jakubowicz *et al.*, 2002). The incidence of pregnancy complications in the second and third trimester among PCOS patients has been only sparsely studied. Gestational diabetes mellitus (GDM), pre-eclampsia (PE), and premature delivery has been associated with PCOS (Diamant *et al.*, 1982; Gjonnaess, 1989; de Vries *et al.*, 1998; Radon *et al.*, 1999; Mikola *et al.*, 2001; Bjercke *et al.*, 2002). At least in Norway, pregnancies in PCOS women are not considered to be high-risk pregnancies.

The use of the anti-diabetic drug metformin in the treatment of non-pregnant PCOS women is quite well established (Wortsman *et al.*, 1991; Velazquez *et al.*, 1994, 1997; Nestler and Jakubowicz, 1997; Morin-Papunen *et al.*, 1998; Moghetti *et al.*, 2000; Pasquali *et al.*, 2000; Fleming *et al.*, 2002). However, the effect of metformin in pregnant women has not been studied in detail. Studies from South Africa found no adverse effects of metformin in pregnant women with GDM (Coetzee and Jackson, 1979, 1984), whereas a non-randomized Danish study reported that metformin treatment was associated with an increased prevalence of PE and high perinatal mortality in diabetic women when compared with sulphonylurea treatment (Hellmuth *et al.*, 2000). This study, however, lasted for decades and the women in the metformin group were significantly more obese than in the control group. An observational study without control group reported a decreased first trimester pregnancy loss among women treated with metformin in early pregnancy (Glueck *et al.*, 2002a), and they also found that metformin therapy throughout pregnancy reduced the incidence of GDM from 40 to 4% in PCOS women (Glueck *et al.*, 2002b).

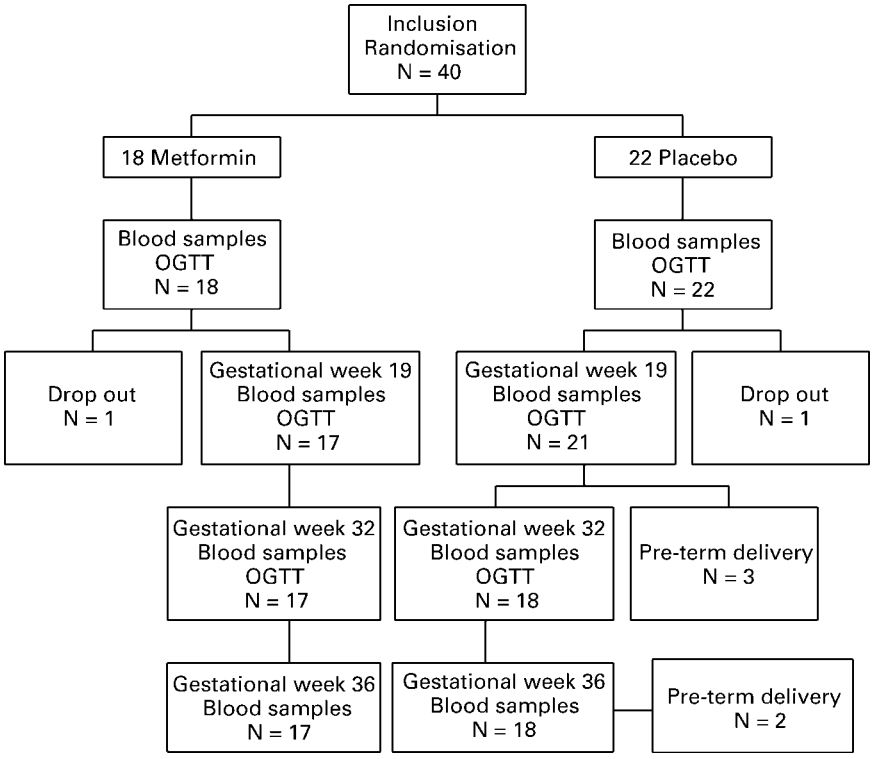

Figure 1. Flowchart on randomization, dropouts and preterm deliveries.

Pregnant PCOS women have higher androgen levels than their age- and weight-matched controls (Sir-Petermann *et al.*, 2002). Elevated androgen levels later in life have been associated with prior pre-eclampsia (Laivuori *et al.*, 1998). In a case report, metformin markedly reduced androgen levels in a hyperandrogenic, pregnant woman who was treated with metformin to prevent masculinization of a female fetus (Sarlis *et al.*, 1999). In monkeys, premature labour and delivery can be induced in the early third trimester with i.v. administration of androstenedione (Mecenas *et al.*, 1996). We hypothesized that metformin would reduce androgen levels in pregnant PCOS women and that reduced androgen levels might, directly or indirectly, influence pregnancy complications and/or pregnancy outcome.

Materials and methods

From October 2000 to March 2003, 40 pregnant women with PCOS were recruited from the gynaecological and the infertility outpatient clinic at The University Hospital of Trondheim. The diagnosis of PCOS was based on the presence of polycystic ovaries (nine or more sub-capsular follicles with a diameter of 3–8 mm) verified by transvaginal ultrasonography. Furthermore at least one of the following five criteria had to be present: testosterone >2.5 nmol/l, sex hormone-binding globulin (SHBG) <30 nmol/l, fasting insulin C-peptide >1.0 nmol/l, oligomenorrhoea (length of menstrual cycle >35 days or <10 periods per year), or hirsutism, judged clinically as male pattern growth of body hair. All the study participants fulfilled the 'Revised 2003 consensus' on diagnostic criteria for PCOS, implying that at least two of the three following criteria were fulfilled: polycystic ovaries, hyperandrogenism (clinical and/or biochemical) and oligo- and/or anovulation (Rotterdam ESHRE/ASRM-sponsored PCOS workshop group, 2004).

The inclusion criteria for the study were: (i) diagnosis of PCOS before the actual pregnancy, (ii) age 18–40 years, (iii) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography.

The exclusion criteria were known liver disease, creatinine >130 mmol/l, known alcohol abuse, previously known diabetes mellitus, fasting plasma glucose >5.6 mmol/l, treatment with oral glucocorticoids or use of drugs known to interfere with metformin. One of the authors (E.V.) enrolled all the participants.

Eighteen women were randomized to metformin medication and 22 to placebo (Figure 1). Two women, one in each group, withdrew within 2 weeks after inclusion. One cited a long distance to the hospital and the other had motivation failure. The remaining 38 women completed the study. The randomization and encapsulation of metformin and placebo to identical capsules were performed at the Trondheim University Hospital Pharmacy.

Randomization was performed with sealed envelopes. The envelopes were ordered in a random manner and given a randomization number by a pharmacist who did not belong to the research group. Randomization was performed in blocks of 10 and women were stratified according to whether or not they used metformin at conception.

At conception, 11 women in the placebo group and eight in the metformin group used metformin. Seven of the women who used metformin at conception (five in the placebo group and two in the metformin group) continued to use it until a few days before inclusion. All women had a 'wash out' period of ≥ 2 days before inclusion. Inclusion, randomization, oral glucose tolerance test (OGTT) and drawing of blood samples occurred on the same day. Study medication was started the next morning.

At randomization (pregnancy week 5–12) and later at gestational week 19, 32 and 36, venous blood samples were drawn from an antecubital vein, between 08:00 and 11:00 after an overnight fast. Blood samples were centrifuged at room temperature within 30 min

and stored at −70°C until analysis (1–28 months). A 75 g OGTT was performed according to the World Health Organization (1998) recommendations at inclusion and at gestational weeks 19 and 32 WHO consultation group (1998), Expert committe (1998).

Blood pressure was measured while the patient was in the sitting position after ≥15 min of rest. The blood pressure was measured three times, ≥2 min apart. The mean of the second and third measurement was calculated. All patients were followed up and treated during pregnancy according to standard antenatal care. A blinded evaluation of all maternal and infant diagnoses was performed by one of the authors (R.H.).

Study protocol

All participants received individual, verbal and written, diet and lifestyle counselling at inclusion. Thereafter treatment with metformin 425 mg (metformin hydrochloride, Metformin®; Weifa AS, Norway) or identical placebo capsules was initiated. All participants used two capsules once daily during the first week and two capsules twice daily for the rest of the study period. In addition, they all received a 1 mg tablet of folate daily, and one daily multivitamin tablet containing: vitamin A 800 mg, vitamin B_1 1.4 mg, vitamin B_2 1.6 mg, vitamin B_6 2 mg, vitamin B_{12} 1 mg, folic acid 200 mg, niacin 18 mg, pantotenic acid 6 mg, vitamin C 60 mg, vitamin D 5 mg, vitamin E 10 mg, Fe^{2+} 14 mg, Zn^{+} 15 mg, Cu^{2+} 2 mg, iodine 150 mg, Mn^{2+} 2.5 mg, Cr^{+} 50 mg, and Se^{+} 50 mg (Vitaplex®; Alpharma AS, Norway).

Primary outcome measures were dehydroepiandrosterone sulphate (DHEAS), androstenedione, testosterone, SHBG and free testosterone index (FTI). Secondary outcome measures were pregnancy outcome and pregnancy complications.

A written informed consent was obtained from each patient before inclusion and the declaration of Helsinki was followed throughout the study. The Committee for Medical Research Ethics of Health Region IV, Norway, and The Norwegian Medicines Agency approved the study.

Assays

Serum glucose was analysed, on the blood sampling day, by a glucose dehydrogenase method after protein precipitation with perchloric acid using the Merck Granutest 250 reagent kit (E.Merck, Germany). The rest of the blood tests were performed in serum. Testosterone and androstenedione were measured by a double antibody technique on an Elecsys 2010 analyser (Roche Diagnostics GmbH, Germany) using reagents and calibrators supplied by the manufacturer. SHBG and DHEAS were measured using a competitive immunoassay on an Immulite 2000 analyser using the reagents and calibrators supplied by the manufacturer (Diagnostic Products Corp., USA). FTI was calculated as total testosterone divided by SHBG and multiplied by a factor of 100. The lower and upper reference values for non-pregnant women were 0.9 and 11.7 mmol/l for DHEAS, 0.7 and 11.0 nmol/l for androstenedione, 0.1 and 2.9 nmol/l for testosterone, and 18 and 114 nmol/l for SHBG. All analyses except for glucose were performed in a single kit on the same day. Gestational diabetes was defined according to World Health Organization (1998) criteria, i.e. 2 h plasma glucose values ≥7.8 mmol/l during an OGTT with 75 g glucose WHO consultation group (1998), Expert committe (1998). Uncomplicated GDM treated with dietary advice only was not ranked among the complications in this study. pH was measured in umbilical artery blood, immediately after delivery on a Rapidlab 248pH/Blood Gas Analyzer, using reagents and calibrators supplied by the manufacturer (Bayer Corp., USA).

Pre-eclampsia was defined as a blood pressure ≥140/90 mmHg with concomitant albuminuria ≥0.3 g/24 h measured on two separate occasions after gestational week 20. Premature delivery was defined as delivery before gestational week 37 + 0 according to an estimated date of delivery, based on mid-trimester ultrasound scan.

Statistical analysis

All statistical procedures were performed using the SPSS version 11.0 for Windows (SPSS Inc., USA). For sample size calculations, we acheived 16–17 patients in each group at 80% power to detect a 1.0 nmol/l difference in change of testosterone level between groups when assuming SD of 1.0 nmol/l. To evaluate treatment effects, the changes in hormone levels from inclusion to week 19, 32 and 36 were calculated for each woman. The differences in change between the study groups were compared with two-tailed *t*-tests for independent samples for normally distributed variables. Non-parametric tests for independent samples were applied for variables with skewed distributions. Fisher's exact test was used for evaluation of discrete data. Values are reported as means (SD). Two-tailed $P < 0.05$ was considered significant. No adjustments for multiple comparisons were performed. Data on pregnancy complications and pregnancy outcome were analysed according to the 'intention to treat' principle.

Table I. Patient characteristics at inclusion

	Placebo ($n = 22$)	Metformin ($n = 18$)	*P*
Age (years)[a]	28.3 (3.7)	28.9 (4.8)	0.7
Body mass index (kg/m^2)[a]	29.3 (8.0)	32.1 (6.1)	0.2
Age at menarche (years)[a]	13.4 (1.4)	13.0 (1.9)	0.4
No.of criteria met[a]	3.5 (1.1)	2.9 (1.1)	0.1
Systolic blood pressure (mmHg)[a]	117 (16)	120 (14)	0.5
Diastolic blood pressure (mmHg)[a]	72 (10)	78 (9)	0.05
Resting heart rate (beats/min)[a]	73 (11)	75 (10)	0.6
Gestational age at inclusion days[a]	55 (17)	59 (14)	0.4
Metformin treatment at conception[b]	11 (50)	8 (44)	0.8
Gestational diabetes mellitus at inclusion[b]	6 (27)	2 (11)	0.3
Patient ever pregnant earlier[b]	11 (50)	11 (61)	0.5
Former pregnancy losses[b]	10 (45)	7 (39)	0.7
Legal abortions[b]	1 (5)	2 (11)	0.4
Former deliveries[b]	11 (50)	7 (39)	0.5

[a]Continuous variables are presented as mean (SD).
[b]Categorical variables are presented as number (%) of participants.

Results

Study population

The mean (± SD) age of the women was 28.6 ± 4.2 years and the mean body mass index (BMI) was 30.6 ± 7.3 kg/m^2 with no significant differences between the study groups (Table I). Seven patients met all five of the additional criteria for PCOS described in the Materials and methods section, and nine met four of the criteria. Eleven and 13 patients met three and two of the criteria respectively, and none met only one criterion. Mean gestational age at inclusion was 56 ± 16 days. Inclusion occurred earliest at gestational week 5 and latest at gestational week 12.

Mean blood pressure was 118/75 mmHg with higher diastolic pressure in the metformin group.

Twenty-two of the 40 women in the study had been pregnant previously, with a total of 38 pregnancies. These pregnancies resulted in 17 (45%) spontaneous abortions, three (8%) legal abortions, and 18 (47%) live-born infants with a mean birthweight of 3560 g and a mean gestational age of 38 weeks.

In the actual pregnancy, seven women conceived spontaneously: three in the placebo and four in the metformin group. Nineteen patients used metformin for ovulation induction when conceiving, 11 in the placebo and eight in the metformin group. Four patients received clomiphene citrate to become pregnant, two in each group, and 10 patients became pregnant after IVF or ICSI, six in the placebo and four in the metformin group.

Androgen levels

At inclusion, androgen levels and SHBG were equal in the two study groups. Further, the change from inclusion to gestational week 19, 32 and 36 did not differ, with respect to DHEAS, androstenedione, testosterone, SHBG or FTI, between the groups (Table II).

Pregnancy complications

Minor pregnancy complications developed in three women in each group (Table III). All these six patients had uncomplicated vaginal deliveries at term and they were discharged from the maternity unit within 4 days post partum.

Severe pregnancy complications were observed only in the placebo group. Five patients had pre-term deliveries (patients 4, 5, 6, 7 and 8). In one woman (patient 7) labour was induced at week 36 + 1 because of severe PE; in the remaining four women spontaneous onset of labour occurred at gestational week 22, 30, 31 and 36 (Table III).

In the post-partum period, serious complications occurred in three women in the placebo group. One woman (patient 8) who was delivered prematurely by emergency Caesarean section (CS) on fetal indication developed endometritis and group A streptococcus sepsis. Another woman (patient 9) developed unexplained acute respiratory distress syndrome (ARDS), after emergency CS on fetal indication. Assisted ventilation was required for 4 days. A third woman (patient 10) with uncomplicated vaginal delivery returned 12 days after discharge from the maternity unit with low abdominal pain and respiratory distress. A large pelvic vein thrombosis and massive lung embolism was diagnosed.

When comparing the number of patients with pregnancy-related complications in the placebo group (10/22, 45%) and in the metformin group (3/18, 17%) (Table III), a tendency towards reduction of complications ($P = 0.09$) was observed in the metformin group. Severe pregnancy-related complications occurred only in the placebo group (7/22; 32% versus 0/18, 0%, $P = 0.01$).

Seven out of 40 women (18%) were delivered by emergency CS, four (18%) in the placebo and three (17%) in the metformin group. The overall CS rate at the University Hospital of Trondheim is currently ~15% and the emergency CS rate is ~9% of all deliveries.

OGTT and gestational diabetes mellitus

None of the women had known diabetes mellitus before conceiving and all had normal fasting plasma glucose at inclusion (range 4.0–5.3 mmol/l). None of the women had been diagnosed with GDM during former pregnancy. At inclusion, prior to any study intervention, eight out of 40

Table II. Changes in maternal androgen levels and body mass index in polycystic ovary syndrome women during pregnancy, according to treatment by metformin or placebo

	Group	Inclusion		Change to week 19		Change to week 32		Change to week 36	
		n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
DHEAS (μmol/l)	Placebo	21	5.3 (3.2)	21	−1.8 (1.8)	18	−2.8 (2.3)	17	−3.1 (2.5)
	Metformin	17	5.3 (2.6)	17	−1.8 (1.0)	17	−2.9 (1.4)	17	−3.3 (1.8)
Androstenedione (nmol/l)	Placebo	21	23.4 (16.6)	21	−0.5 (16.6)	18	8.9 (27.5)	17	16.8 (28.5)
	Metformin	17	20.0 (5.8)	17	1.6 (5.7)	17	3.7 (4.1)	17	13.1 (10.6)
Testosterone (nmol/l)	Placebo	21	4.2 (2.6)	21	−1.0 (2.4)	18	−0.0 (5.1)	17	0.4 (5.0)
	Metformin	17	3.7 (1.5)	17	−0.8 (1.1)	17	−0.9 (1.1)	17	−0.3 (1.3)
SHBG (nmol/l)	Placebo	21	145 (100)	21	136 (72)	18	195 (82)	17	220 (86)
	Metformin	17	128 (60)	17	162 (81)	17	211 (85)	17	239 (88)
Free testosterone index	Placebo	21	4.3 (3.8)	21	−3.0 (3.4)	18	−3.2 (3.9)	17	−3.4 (3.9)
	Metformin	17	3.7 (2.6)	17	−2.7 (2.5)	17	−2.8 (2.4)	17	−2.7 (2.4)
Body mass index (kg/m^2)	Placebo	21	29.4 (8.2)	21	0.6 (13)	18	2.6 (1.8)	17	3.2 (1.8)
	Metformin	17	32.0 (6.3)	16	0.0 (1.3)	16	1.7 (1.9)	16	2.4 (2.1)

Reference values for non-pregnant women: dehydroepiandrosterone sulphate (DHEAS), 0.9-11.7 μmol/l; androstenedione, 0.7–11.0 nmol/l; testosterone, 0.0–2.9 nmol/l; sex hormone-binding globulin (SHBG), 18–114 nmol/l.

Table III. Complications in pregnancies of polycystic ovary syndrome women according to treatment by metformin or placebo during pregnancy

	Placebo group ($n = 22$)		Metformin group ($n = 18$)	
	Patient no.	Complication	Patient no.	Complication
Minor complications in pregnancy	1	Insulin-requiring GDM from week 27; vaginal term delivery	23	PE and GDM; vaginal term delivery
	2	Insulin-requiring GDM from week 32; vaginal term delivery	24	Mild PE from week 37; vaginal term delivery
	3	PE and GDM; vaginal term delivery	25	Mild hypertension from week 38; vaginal term delivery
Major complications in pregnancy	4	Pre-term delivery, week 22; cervical insufficiency		
	5	Pre-term delivery, week 29 + 1; cervical insufficiency		
	6	Pre-term delivery, week 30 + 6; PROM from week 26 + 2		
	7	Pre-term delivery, week 36 + 1; severe PE		
	8	Pre-term delivery, week 36 + 4		
Major complications post partum	8	Group A streptococcus sepsis after CS		
	9	ARDS and assisted ventilation after CS		
	10	Pelvic deep vein thrombosis and massive lung embolism		

GDM = gestational diabetes mellitus; PE = pre-eclampsia; PROM = premature rupture of membranes; CS = Caesarean section; ARDS = acute respiratory distress syndrome.

patients (20%) had 2 h plasma glucose levels ≥ 7.8 mmol/l, at OGTT. After the initial OGTT, two of these patients were randomized to the metformin group and six patients to the placebo group. Thus, according to the WHO criteria, these eight patients had GDM already at the time of inclusion. Another three patients had elevated 2 h plasma glucose values at gestational week 19, two in the metformin group and one in the placebo group. At gestational week 32, another six patients showed pathological 2 h plasma glucose values, four in the metformin and two in the placebo group. In all, 17 (42%) pregnant women with PCOS met the criteria for GDM through pregnancy, nine in the placebo group and eight in the metformin group. All of these patients were treated with additional diet and lifestyle advice and self-monitoring of blood glucose. Two women in the placebo group and none in the metformin group required additional treatment with insulin. Insulin therapy was considered necessary if self-monitored fasting blood glucose was >5.5 mmol/l and/or the 1 h postprandial blood glucose was >8.0 mmol/l on more than two occasions. The aims of the insulin therapy were to keep the fasting blood glucose values ≤ 5.5 mmol/l and the 1 h glucose values ≤ 8.0 mmol/l (Metzger and Coustan, 1998; Jovanovic and Pettitt, 2001).

Metformin tolerability

None of the 38 women completing the study stopped the study medication. Six patients, three in each group, reported persistent nausea and gastrointestinal discomfort. They were instructed to reduce medication intake to one capsule twice daily.

Infants

The difference in gestational age, gestational length, head circumference and birthweight between the groups did not reach statistical significance. Placental weight, Apgar scores at 5 and 10 min, and pH of the umbilical vein did not differ between the groups (Table IV). No major anatomical malformations were observed. Minor anatomical abnormalities were seen in seven infants. In the placebo group there were two infants with pes equino-varus (patients 1 and 12), one with bilateral cryptorchidism (patient 10) and one with a large haemangioma on the hip (patient 11). In the metformin group

Table IV. Infant outcomes in pregnancies of polycystic ovary syndrome women according to treatment by metformin or placebo during pregnancy

	Placebo		Metformin		*P*
	n	Mean (SD)	*n*	Mean (SD)	
Gestational age at birth (days)	22	266 (36)	18	282 (8)	0.06
Gestational length (cm)	22	48 (8)	18	50 (2)	0.2
Head circumference (cm)	21	34 (5)	18	36 (1)	0.07
Birthweight (g)	22	3215 (1048)	18	3595 (420)	0.1
Placental weight (g)	21	584 (172)	18	571 (127)	0.8
Apgar score at 5 min	21	9.5 (0.6)	18	9.3 (1.0)	0.3
Apgar score at 10 min	21	9.9 (0.2)	18	9.8 (0.7)	0.3
Umbilical artery pH	13	7.26 (0.07)	18	7.24 (0.10)	0.5

there were two infants with a periauricular adnex (patients 24 and 26) and one with unilateral cryptorchidism (patient 27).

Discussion

In contrast to our hypothesis, metformin did not reduce androgen levels in PCOS women during pregnancy. Maternal testosterone levels were more or less unaltered throughout pregnancy, while FTI decreased markedly from inclusion to gestational week 19 in both groups ($P < 0.005$), due to increased SHBG levels in the second and third trimester of pregnancy. Hence, metformin treatment had no major effect on androgen or SHBG levels in the present study. This result is in contrast to a case report on a hyperandrogenic woman treated with metformin sequentially during pregnancy (Sarlis *et al.*, 1999). In a recent study, Glueck *et al.* (2004) concludes that metformin reduces testosterone levels in pregnant PCOS women. In that study, women were treated with metformin and calorie restrictions preconceptionally, and metformin was continued throughout pregnancy. Glueck *et al.* found decreased testosterone levels during pregnancy compared to preconceptional levels and concluded that metformin reduces maternal testosterone levels in pregnant PCOS women. They found that testosterone rose in the first trimester and showed slight alterations throughout pregnancy (Glueck *et al.*, 2004). We reproduce this finding of decreasing testosterone levels from first to second trimester and then somewhat increasing in the third trimester of pregnancy. However, this was observed both in the metformin and placebo groups. This indicates that the decrease in androgens is inherent to pregnancy and/or diet and lifestyle intervention in PCOS women, and has probably little or nothing to do with metformin.

Severe pregnancy complications were significantly less frequent in the metformin group than in the placebo group. Although pregnancy complications and outcomes were secondary outcome measures, this must be regarded as the most important observation of our study. A remarkable finding is the occurrence of five premature deliveries (23%) in the placebo group. We can offer no explanation to this observation.

Pre-study metformin treatment could theoretically have influenced our results. However, the stratification was specifically aimed to control for pre-randomization use of metformin. It is hence unlikely that pre-randomization use of metformin influenced our data with respect to androgen levels or other parameters in the two treatment groups. In the present study, we found that 20% of the women fulfilled the criteria for GDM already at the time of inclusion, around the eighth week of pregnancy. The present study was neither designed nor powered to investigate the effects of metformin on the incidence of GDM. However, the total GDM incidence of 42% throughout pregnancy supports earlier observations of a high prevalence of GDM in PCOS patients (Radon *et al.*, 1999; Mikola *et al.*, 2001). Our finding in a randomized controlled design does not support a 90% reduction of GDM by metformin in PCOS women reported by Glueck *et al.* (2002b). The discrepancy, in the findings and conclusions, of the present study and the studies by Glueck *et al.* with regard to the metformin effect on maternal androgen levels and GDM are noteworthy. We believe that this underlines the importance of performing prospective, randomized, placebo-controlled studies in conditions where diet and lifestyle intervention is known or suspected to affect the outcome or where the natural course of the disease is sparsely investigated. However, the results of the present study should be interpreted with caution due to the limited number of participants.

If our results are representative for pregnancies in PCOS women, one might speculate why the high frequency of complications is not a well-known phenomenon among clinicians. Possibly, when women present in mid and late pregnancy the physicians pay less attention to former irregular menstruations, centralized adiposity, and hirsutism. Another possible explanation for the frequent complications might be the high percentage of assisted fertilization, ovulation stimulation and metformin use at conception, indicating that our patients might represent a group of PCOS women with more extreme metabolic and endocrine changes than the average women with PCOS.

Although mean BMI was not significantly different between the placebo and metformin groups, it was distributed unevenly between groups. Eleven of the women in the placebo group versus four in the metformin group had a BMI $< 30\,kg/m^2$. High BMI is associated with increased incidence of pregnancy complications. Since theoretically it would give more complications in the metformin group, not in the control group, this should only lead to conservative estimates of effect. As we had five premature deliveries in the placebo group, weight gain differences between the groups through pregnancy is difficult to interpret.

Nausea and mild gastrointestinal discomfort are common complaints in pregnancy. The most frequent side-effect of metformin is also gastrointestinal discomfort Physician Desk Reference (1999). Hence, we anticipated that metformin might enforce nausea and vomiting in pregnant PCOS women. However, metformin 850 mg twice daily was well tolerated and dose reduction was seldom necessary. Lactoacidosis is a rare but serious complication of metformin treatment. Whether metformin passes from the mother to the fetus in humans is not known. If it does, it is reassuring that we were unable to detect an effect on umbilical artery pH at birth. This indicates that maternal metformin treatment does not lead to lactic acidosis in the fetus.

We conclude that metformin treatment appears to be safe in pregnant PCOS women. It does not affect maternal androgen levels and is well tolerated. Severe pregnancy complications seem to be prevented by metformin in PCOS patients. If our data are confirmed by future studies, metformin might become a safe and inexpensive treatment for prevention of mid and late pregnancy complications in women with PCOS. Hence, sufficiently powered, randomized, clinical trials should be initiated to study the effect of metformin treatment on the different pregnancy complications associated with PCOS.

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References

Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S and Escobar-Morreale HF (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 85,2434–2438.

Balen AH, Tan SL, MacDougall J and Jacobs HS (1993) Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum Reprod 8,959–964.

Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G and Abyholm T (2002) Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. Gynecol Obstet Invest 54,94–98.

Clifford K, Rai R, Watson H and Regan L (1994) An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Hum Reprod 9,1328–1332.

Coetzee EJ and Jackson WP (1979) Metformin in management of pregnant insulin-independent diabetics. Diabetologia 16,241–245.

Coetzee EJ and Jackson WP (1984) Oral hypoglycaemics in the first trimester and fetal outcome. S Afr Med J 65,635–637.

de Vries MJ, Dekker GA and Schoemaker J (1998) Higher risk of preeclampsia in the polycystic ovary syndrome. A case control study. Eur J Obstet Gynecol Reprod Biol 76,91–95.

Diamant YZ, Rimon E and Evron S (1982) High incidence of preeclamptic toxemia in patients with polycystic ovarian disease. Eur J Obstet Gynecol Reprod Biol 14,199–204.

Expert committee (1998) Report of the expert committee on diagnosis and classification of diabetes mellitus. Diabetes Care, pp. S5–S19.

Fleming R, Hopkinson ZE, Wallace AM, Greer IA and Sattar N (2002) Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab 87,569–574.

Franks S (1995) Polycystic ovary syndrome. N Engl J Med 333,853–861.

Gjonnaess H (1989) The course and outcome of pregnancy after ovarian electrocautery in women with polycystic ovarian syndrome: the influence of body-weight. Br J Obstet Gynaecol 96,714–719.

Glueck CJ, Wang P, Goldenberg N and Sieve-Smith L (2002a) Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod 17,2858–2864.

Glueck CJ, Wang P, Kobayashi S, Phillips H and Sieve-Smith L (2002b) Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil Steril 77,520–525.

Glueck CJ, Goldenberg N, Wang P, Loftspring M and Sherman A (2004) Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. Hum Reprod 19, 510–521.

Hellmuth E, Damm P and Molsted-Pedersen L (2000) Oral hypoglycaemic agents in 118 diabetic pregnancies. Diabet Med 17,507–511.

Homburg R, Armar NA, Eshel A, Adams J and Jacobs HS (1988) Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. Br Med J 297, 1024–1026.

Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA and Nestler JE (2002) Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 87,524–529.

Jovanovic L and Pettitt DJ (2001) Gestational diabetes mellitus. J Am Med Assoc 286,2516–2518.

Laivuori H, Kaaja R, Rutanen EM, Viinikka L and Ylikorkala O (1998) Evidence of high circulating testosterone in women with prior preeclampsia. J Clin Endocrinol Metab 83,344–347.

Mecenas CA, Giussani DA, Owiny JR, Jenkins SL, Wu WX, Honnebier BO, Lockwood CJ, Kong L, Guller S and Nathanielsz PW (1996) Production of premature delivery in pregnant rhesus monkeys by androstenedione infusion. Nat Med 2,443–448.

Metzger BE and Coustan DR (1998) Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 21 (Suppl 2),B161–B167.

Mikola M, Hiilesmaa V, Halttunen M, Suhonen L and Tiitinen A (2001) Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod 16,226–229.

Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, Zanolin E and Muggeo M (2000) Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab 85,139–146.

Morin-Papunen LC, Koivunen RM, Ruokonen A and Martikainen HK (1998) Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. Fertil Steril 69,691–696.

Nestler JE and Jakubowicz DJ (1997) Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. J Clin Endocrinol Metab 82, 4075–4079.

Okon MA, Laird SM, Tuckerman EM and Li TC (1998) Serum androgen levels in women who have recurrent miscarriages and their correlation with markers of endometrial function. Fertil Steril 69,682–690.

Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M and Morselli-Labate AM (2000) Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 85,2767–2774.

Physician Desk Reference (1999) Product information edn. Medical Economic Company Inc.

Radon PA, McMahon MJ and Meyer WR (1999) Impaired glucose tolerance in pregnant women with polycystic ovary syndrome. Obstet Gynecol 94, 194–197.

Regan L, Owen EJ and Jacobs HS (1990) Hypersecretion of luteinising hormone, infertility, and miscarriage. Lancet 336,1141–1144.

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19, 41–47.

Sagle M, Bishop K, Ridley N, Alexander FM, Michel M, Bonney RC, Beard RW and Franks S (1988) Recurrent early miscarriage and polycystic ovaries. Br Med J 297,1027–1028.

Sarlis NJ, Weil SJ and Nelson LM (1999) Administration of metformin to a diabetic woman with extreme hyperandrogenemia of nontumoral origin: management of infertility and prevention of inadvertent masculinization of a female fetus. J Clin Endocrinol Metab 84,1510–1512.

Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Perez-Bravo F and Recabarren SE (2002) Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Hum Reprod 17,2573–2579.

Tulppala M, Stenman UH, Cacciatore B and Ylikorkala O (1993) Polycystic ovaries and levels of gonadotrophins and androgens in recurrent miscarriage: prospective study in 50 women. Br J Obstet Gynaecol 100, 348–352.

Velazquez E, Acosta A and Mendoza SG (1997) Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 90, 392–395.

Velazquez EM, Mendoza S, Hamer T, Sosa F and Glueck CJ (1994) Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 43,647–654.

World Health Organization (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation Group.

Wortsman J, de Angeles S, Futterweit W, Singh KB and Kaufmann RC (1991) Gestational diabetes and neonatal macrosomia in the polycystic ovary syndrome. J Reprod Med 36,659–661.

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