Metformin *Versus* Placebo from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study

Eszter Vanky, Solhild Stridsklev, Runa Heimstad, Pål Romundstad, Kristin Skogøy, Odrun Kleggetveit, Sissel Hjelle, Philip von Brandis, Torunn Eikeland, Karin Flo, Kristin Flaten Berg, Gabor Bunford, Agnethe Lund, Cecilie Bjerke, Ingunn Almås, Ann Hilde Berg, Anna Danielson, Gulim Lahmami, and Sven Magnus Carlsen*

Context: Metformin is widely prescribed to pregnant women with polycystic ovary syndrome (PCOS) in an attempt to reduce pregnancy complications. Metformin is not approved for this indication, and evidence for this practice is lacking.

Objectives: Our objective was to test the hypothesis that metformin, from first trimester to delivery, reduces pregnancy complications in women with PCOS.

Design and Setting: We conducted a randomized, placebo-controlled, double-blind, multicenter study at 11 secondary care centers.

Participants: The participants were 257 women with PCOS, in the first trimester of pregnancy, aged 18–42 yr.

Intervention: We randomly assigned 274 singleton pregnancies (in 257 women) to receive metformin or placebo, from first trimester to delivery.

Main Outcome Measures: The prevalence of preeclampsia, gestational diabetes mellitus, preterm delivery, and a composite of these three outcomes is reported.

Results: Preeclampsia prevalence was 7.4% in the metformin group and 3.7% in the placebo group (3.7%; 95% CI, $-1.7–9.2$) ($P = 0.18$). Preterm delivery prevalence was 3.7% in the metformin group and 8.2% in the placebo group (-4.4%; 95%, CI, $-10.1–1.2$) ($P = 0.12$). Gestational diabetes mellitus prevalence was 17.6% in the metformin group and 16.9% in the placebo group (0.8%; 95% CI, $-8.6–10.2$) ($P = 0.87$). The composite primary endpoint prevalence was 25.9 and 24.4%, respectively (1.5%; 95% CI, $-8.9–11.3$) ($P = 0.78$). Women in the metformin group gained less weight during pregnancy compared with those in the placebo group. There was no difference in fetal birth weight between the groups.

Conclusions: Metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS. (*J Clin Endocrinol Metab* 95: E448–E455, 2010)

The polycystic ovary syndrome (PCOS) affects some 8–11% of women in the reproductive age group diagnosed according to National Institutes of Health criteria (NIH) (1–3), and probably up to 15–20% according to the Rotterdam consensus criteria. Its cornerstones are insulin resistance and hyperandrogenicity,

although none is mandatory for the diagnosis according to the Rotterdam criteria (4). PCOS has implications both for fertility and pregnancy outcome, whereas an increasing body of evidence points to a high prevalence of pregnancy complications (5–9). Hyperinsulinemia and hyperandrogenism have been suggested as patho-

Abbreviations: BMI, Body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial.

genic factors in both PCOS and pregnancy complications (10–12).

Metformin, an insulin sensitizer used in the treatment of type 2 diabetes, reduces fasting insulin and testosterone levels in nonobese, nonpregnant PCOS women (13). During the last decade, several retrospective and nonrandomized studies have reported beneficial effects of metformin on pregnancy loss and pregnancy complications, in particular gestational diabetes mellitus (GDM) (5, 9, 14–19), whereas our own small randomized placebo-controlled study showed an overall reduction in pregnancy complications (20). Hence, we designed a larger study to test the hypothesis that metformin use in PCOS pregnancy reduces preeclampsia, preterm delivery, and/or GDM.

Subjects and Methods

Study design

The metformin treatment in pregnant PCOS women (PregMet) study was a prospective, randomized, double-blind, multicenter trial comparing metformin 2000 mg daily with placebo.

The inclusion criteria were 1) PCOS diagnosed according to the Rotterdam criteria (4), 2) age 18–45 yr, 3) gestational age between 5 and 12 wk, and 4) a singleton viable fetus shown on ultrasonography. The exclusion criteria were alanine aminotransferase higher than 90 IU/liter, serum creatinine concentration higher than 1.70 mg/dl, known alcohol abuse, previously diagnosed diabetes mellitus or fasting serum glucose higher than 126 mg/dl at the time point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin.

The diagnosis of PCOS was based on documentation before the actual pregnancy, all diagnosed by a gynecologist. The participants were included at 11 study centers: three university hospitals, seven local hospitals, and one gynecological specialist practice. Before inclusion, women who met the PCOS criteria of the Rotterdam consensus were screened with vaginal ultrasound to confirm a single viable fetus and gestational age. Fasting plasma glucose concentrations, creatinine, and alanine aminotransferase were determined to exclude overt diabetes mellitus or kidney or liver disease before inclusion in the study. Three hundred forty-eight PCOS women with a total of 364 pregnancies were informed about the study (16 women participated twice); 32 did not meet inclusion criteria, and 58 declined to participate. Two hundred seventy-four pregnancies were included and randomized (Fig. 1).

At inclusion, vaginal ultrasonography, drawing of fasting blood samples, and a 75-g oral glucose tolerance test (OGTT) were performed before randomization. Two hundred seventy-four pregnancies (in 258 women) were randomly assigned to either metformin or placebo treatment. In one patient, a partial 21-hydroxylase deficiency had been overlooked, but she was excluded after randomization.

Randomization

Randomization was performed at the Trondheim University Hospital Pharmacy in blocks of 10 (five metformin and five placebo) and stratified according to metformin use at conception. The method was random drawing of an envelope (ordered in groups of 10: five metformin and five placebo) by two pharmacy employees, one executing the drawing and the other monitoring the drawing.

Blinding

The enrolling doctor at the study centers faxed patient details to the university pharmacy. The participants were allotted to placebo or metformin, and the study medication was subsequently mailed to the participants. The participants and care providers were blinded for treatment allocation.

Women who used metformin at conception and in early pregnancy had a washout period of at least 7 d before inclusion in the study. All participants received written and individual verbal counseling on diet and lifestyle at inclusion. Thereafter, treatment with metformin 500 mg (metformin hydrochloride, Metformin, Weifa AS, Oslo, Norway) or identically coated placebo tablets was initiated. The participants were instructed to take one tablet twice daily during the first week and two tablets twice daily for the rest of the study period. To counteract a possible metformin action on vitamin B levels, patients were advised to take 0.8 mg folate daily and one daily multivitamin tablet containing 800 μg vitamin A, 1.4 mg vitamin B_1, 1.6 mg vitamin B_2, 2 mg vitamin B_6, 1 μg vitamin B_{12}, 200 μg folic acid, 18 mg niacin, 6 mg pantothenic acid, 60 mg vitamin C, 5 μg vitamin D, 10 mg vitamin E, 14 mg Fe^{2+}, 15 mg Zn^+, 2 mg Cu^{2+}, 150 μg iodine, 2.5 mg Mn^{2+}, 50 μg Cr^+, and 50 μg Se^+ (Vitaplex; Alpharma AS, Oslo, Norway).

Standardized interviewer-administered questionnaires were used to obtain self-reported data on former medical and gynecological/obstetric history, ethnicity, employment, smoking habits, study medication, and concomitant medication. Biometric variables, including height (measured only at inclusion), weight, blood pressure, and heart rate, were recorded at inclusion and at each prescheduled visit at gestational wk 19, 24, 32, and 36. Fasting blood samples were directly analyzed at each study center for plasma glucose. An OGTT (75 g glucose) was performed at inclusion and gestational wk 19 and 32.

The Committee for Medical Research Ethics of Health Region IV, Norway, and The Norwegian Medicines Agency approved the study. Written informed consent was obtained from each patient before inclusion, and the declaration of Helsinki was followed throughout the study. The study was conducted according to principles of Good Clinical Practice, and the trial is registered at www.clinicaltrials.gov as NCT00159536.

Measurements

Venous blood samples were drawn from an antecubital vein between 0800 and 1100 h after an overnight fast. Blood samples were collected and processed at each study site in accordance
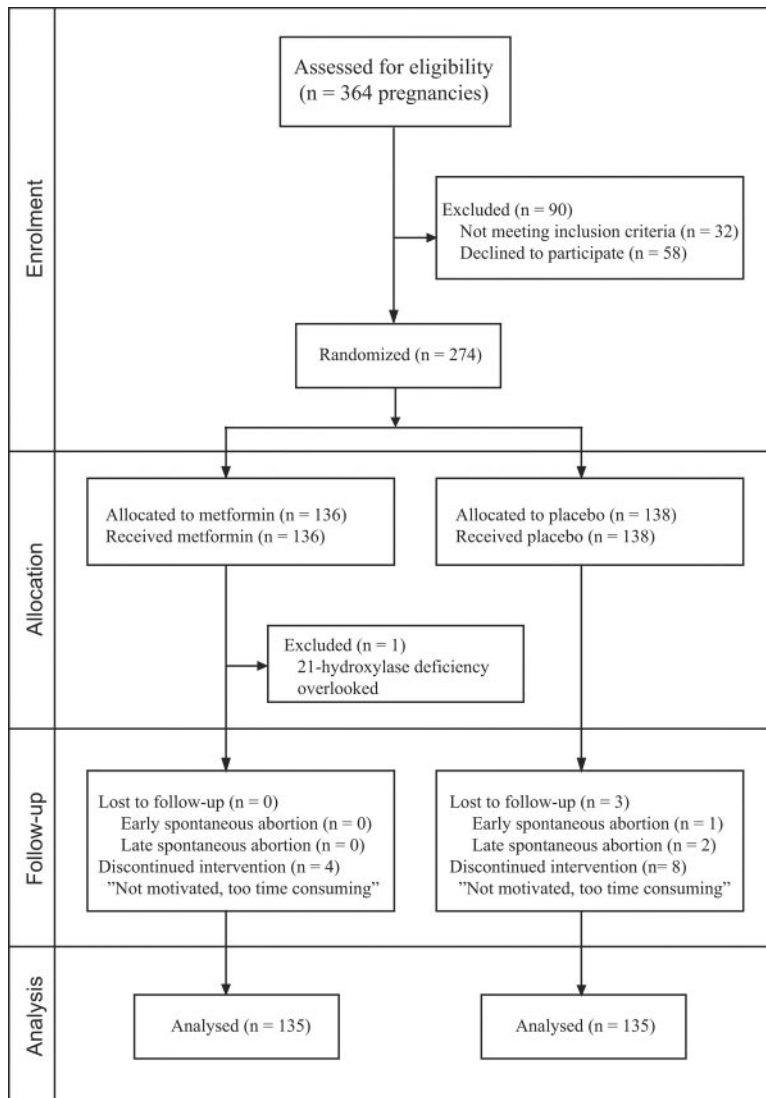
Departments of Obstetrics and Gynecology (E.V., S.S., R.H.) and Endocrinology (S.M.C.), St. Olav's Hospital, Trondheim University Hospital, 7006 Trondheim, Norway; Institute for Laboratory Medicine (E.V., S.S., R.H.), Children's and Women's Health; Department of Public Health (P.R.) and Unit of Applied Clinical Research (S.M.C.), Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, 7489 Trondheim, Norway; Sentral Hospital of Northern Norway (K.S.), 8092 Bodø, Norway; Elvebredden Gynekologpraksis (O.K.), 4630 Kristiansand, Norway; Ålesund Hospital (S.H.), 6026 Ålesund, Norway; Stavanger University Hospital (P.v.B.), 4011 Stavanger, Norway; Haugesund Hospital (T.E.), 5504 Haugesund, Norway; Institute of Clinical Medicine (K.F.), University of Tromsø, 9037 Tromsø, Norway; Buskerud Hospital (K.F.B., I.A.), 3004 Drammen, Norway; Ringerike Hospital (G.B.), 5311 Hønefoss, Norway; University Hospital of Bergen (A.L.), 5053 Bergen, Norway; Lillehammer Hospital (C.B., A.H.B., A.D.), 2629 Lillehammer, Norway

FIG. 1. Patient flow through study.

with local standardized manual of operation. A 75-g OGTT was performed according to the World Health Organization (1998) recommendations (21, 22). Blood pressure and heart rate were measured while the patient was in the sitting position after at least 10 min of comfortable rest in a chair. The blood pressure and heart rate were measured three times, 2 min apart, with digital devices. The mean of the second and third measurements was calculated. Body weight was recorded with light clothes on and without shoes. Gestational age was determined by examination with vaginal ultrasonography, measuring crown-rump length and/r bi-parietal diameter of the fetus.

Outcomes

Primary endpoints of the trial were the prevalence of preeclampsia, preterm delivery, GDM, and a composite of these three diagnoses. Preeclampsia was diagnosed as blood pressure of 140/90 mm Hg or higher measured on two occasions after gestational wk 20 and albuminuria of at least +2 dipstick on one occasion or +1 dipstick on two occasions. Preterm delivery was defined as delivery before gestational wk 37, based on midpregnancy ultrasound scan, performed during gestational wk 17–20.

GDM was diagnosed as fasting plasma glucose higher than 126 mg/dl and/or 2-h serum glucose higher than 140 mg/dl after an OGTT (75 g glucose solved in 300 ml water). Insulin treatment was considered if plasma glucose levels 1–1.5 h after meal were higher than 144 mg/dl (8 mmol/liter). Composite endpoints were calculated as a participant having one or more of the three above mentioned pregnancy complications. The choice of preterm delivery as a primary outcome was based on the findings in our randomized controlled pilot study (20) and reports from other authors finding increased incidents of preterm delivery among PCOS women (5–8).

Secondary outcomes included weight, blood pressure, heart rate, and mode and length of delivery. Serious adverse events were defined as fatal events to mother or offspring, life-threatening conditions, or events that required prolonged hospitalization.

Protocol deviation

Because of time elapsed between information about the study, clinical examination, and inclusion, 18 women (11 in the metformin and seven in the placebo group) were included later in pregnancy than intended, *i.e.* between gestational wk13 and 15.

Compliance

Participants were asked about their intake of study medication at prescheduled visits in gestational wk 19, 24, 32, and 36 and at delivery. Dose reductions or stops were recorded. From these records we divided participants into three categories: good compliance, defined as medication taken as intended; acceptable compliance, defined as reduced medication to one to two tablets per day for a maximum of 4 wk and/or no tablets for a maximum 2 wk, otherwise as intended; and poor compliance, defined as reduced medication to one to two tablets per day more than 4 wk and/or no tablets more than 2 wk.

Data management

All data entry, data management, and data analyses were performed at the Institute of Laboratory Medicine, Children's and Women's Health and Institute of Public Health, Norwegian University of Science and Technology. The first participant was included in February 2005 and the last in January 2009. The last patient gave birth in August 2009. Data were analyzed according to intention to treat. Twelve women dropped out, *i.e.* discontinued medication and did not turn up at scheduled visits. They gave consent that data from their hospital records about pregnancy, delivery, and postpartum period could be included in the analyses. Participants and all investigators were blinded to group assignment. One of the authors (R.H.) evaluated and quality

checked (blinded) all outcomes and diagnoses. Other authors (E.V., P.R., and S.M.C.) analyzed the data.

Statistical analysis

The sample size calculation was based on the results of our pilot study to detect a 25% difference in preterm deliveries and insulin-requiring GDM (20). With at least 90% probability, we needed 152 women in each group. Because of the expiry date of the study drug batch, inclusion closed when 274 pregnancies had been included and randomized. The inclusion rate declined in the last 18 months of the study, probably because metformin became more available for pregnant PCOS women.

The data were analyzed according to the intention-to-treat principle using Stata software version 10.0 for Windows (Stata Corp., College Station, TX). Binomial regression was used to calculate difference in risk of pregnancy complications by treatment group. The estimated risk differences were accompanied with 95% confidence intervals (CI) and corresponding P values. We also analyzed the data per protocol.

For repeated measurements during pregnancy (*i.e.* systolic and diastolic blood pressure, heart rate, and maternal weight), we used a random-effects model where we adjusted for the baseline values and treated week of pregnancy (wk 19, 25, 32, and 36) as dummy variables. The lincom command was used to estimate mean values with 95% CI in each group according to treatment and pregnancy week.

Categorical variables are presented as a frequency and percentage in each group. A χ^2 test was used to test differences between the groups. If the smallest expected value in a cell was less than five, we used the Fisher exact test. All tables, figures, and statistical procedures including *post hoc* analyses were performed before the randomization code was broken.

Role of the funding source

The Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology, who was funding the study, or Weifa AS, who supplied the study drug free of charge, had no role in the collection, analysis, and interpretation of the data or writing the report and deciding to submit the paper.

Results

Study population

Baseline characteristics were not significantly different in the two study groups (Table 1). During the study, eight women dropped out immediately after inclusion (three in the metformin group and five in the placebo group) and four (one in the metformin group and three in the placebo group) after gestational wk 24 (Fig. 1). The reasons given were lack of motivation, long distance to the investigating center, and time-consuming procedures. None dropped out because of side effects. Three women in the placebo group were lost to follow-up because of miscarriages.

TABLE 1. Baseline characteristics of the participants

	Metformin[a] (n = 135)	Placebo[a] (n = 138)
Age (yr)	29.6 (4.4)	29.2 (4.4)
Weight (kg)	82.5 (20.1)	79.3 (18.0)
BMI (kg/m²)	29.5 (7.0)	28.5 (7.2)
Systolic blood pressure (mm Hg)	119 (12)	118 (11)
Diastolic blood pressure (mm Hg)	74 (12)	73 (10)
Heart rate (beats/min)	76 (10)	74 (10)
Fasting glucose (mg/dl)	83 (9)	83 (11)
2-h glucose (mg/dl)	101 (27)	101 (29)
Gestational length at inclusion (d)	74 (13)	75 (11)
GDM at inclusion (no.)	10 (7.4)	13 (9.4)
Metformin use at conception (no.)	45 (33.3)	42 (30.4)
Mode of conception (no.)		
Spontaneous	77 (57.0)	80 (58.0)
Clomiphene citrate	40 (29.6)	31 (22.5)
IVF/ICSI	18 (13.3)	22 (15.9)
Others	0 (0)	5 (3.6)
Parity (no.)		
0	77 (57.0)	77 (55.8)
1	47 (34.8)	45 (32.6)
2+	11 (8.2)	16 (11.6)
Experienced spontaneous abortions (no.)[b]	45 (58)	49 (56)
NIH criteria met (no.)	86 (63.7)	88 (63.8)
Only Rotterdam criteria met (no.)	49 (36.3)	50 (36.2)
Smoking (no.)	14 (10.4)	9 (6.6)
Caucasian (no.)	130 (96.3)	136 (98.6)

Values are given in means and SD or total number (%). NIH criteria for PCOS are hyperandrogenism (clinical or biochemical) and ovulatory dysfunction in the absence of congenital adrenal hyperplasia. ICSI, Intracytoplasmic sperm injection; IVF, *in vitro* fertilization.

[a] No statistical differences between the groups.

[b] Percentage of the women who have been pregnant before.

TABLE 2. Primary endpoints

	Metformin [n (%)]	Placebo [n (%)]	Risk difference (%)	95% CI	*P* value
Preeclampsia	10/135 (7.4)	5/135 (3.7)	3.7	−1.7–9.2	0.18
Preterm delivery[a]	5/135 (3.7)	11/135 (8.2)	−4.4	−10.1–1.2	0.12
New GDM	22/125 (17.6)	21/124 (16.9)	0.8	−8.6–10.2	0.87
Composite primary endpoints	35/135 (25.9)	33/135 (24.4)	1.5	−8.9–11.3	0.78

New GDM was diagnosed after inclusion in the study. Composite endpoints were calculated as follows: if one patient had two complications, it was counted as one composite outcome.

[a] Spontaneous preterm labor included four in the metformin group and six in the placebo group. Preterm delivery on maternal or fetal indications included one in the metformin group and five in the placebo group.

Primary outcomes

There were no differences between the groups in the prevalence of preeclampsia, preterm delivery, GDM, or the composite of these three pregnancy complications (Table 2).

Secondary outcomes

Adjusted for weight at inclusion, women in the metformin group gained less weight from inclusion to wk 36 (−2.2 kg) compared with the placebo group ($P = 0.001$) (Fig. 2A). We found no differences between changes over time in the groups in systolic blood pressure ($P = 0.09$), diastolic blood pressure ($P = 0.29$), or heart rate ($P = 0.30$) from inclusion to wk 36 in pregnancy (Fig. 2, B–D). The length and mode of delivery and blood loss were also similar in the two groups (Table 3). Three patients had insulin-requiring GDM, all in the placebo group.

Other treatment effects

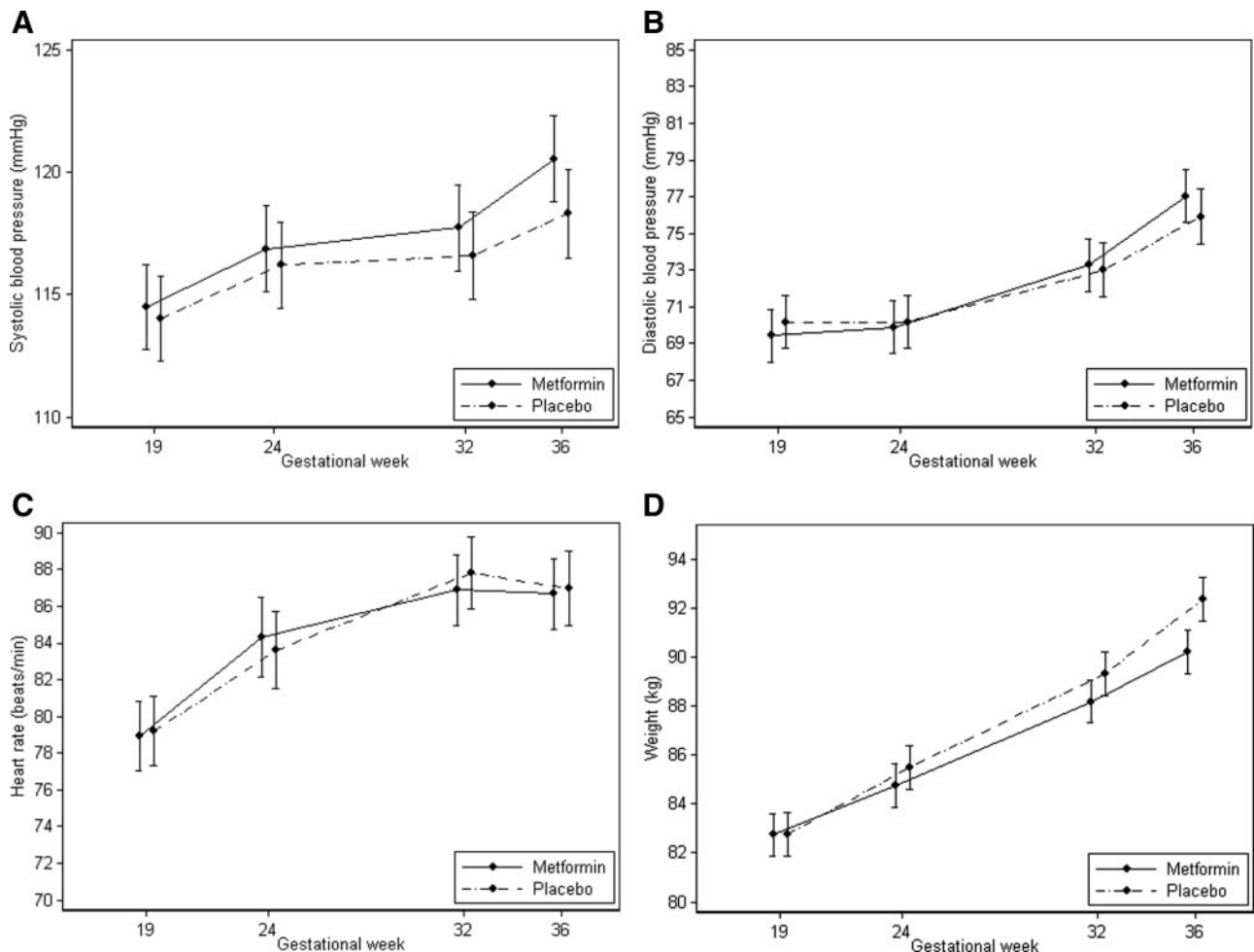We found no differences in birth weight, birth length, ponderal index, APGAR score, umbilical artery pH, and

FIG. 2. Weight, heart rate, and blood pressure development through pregnancy according to study group. The weight, heart rate, and systolic and diastolic blood pressure at inclusion are adjusted for, to show the difference in development through pregnancy. The x-axis is skewed.

TABLE 3. Secondary endpoints and neonatal outcomes in the metformin and placebo group

	Metformin	**Placebo**	*P* value
Labor onset [n (%)]			0.52
Spontaneous	97/130 (74.6)	91/128 (72.1)	
Induced	33/130 (25.4)	37/128 (27.9)	
Mean length of labor (h) (SD)			
All	6.3 (4.6)	5.7 (3.9)	0.28
Vaginal delivery	5.4 (3.3)	5.0 (3.5)	0.40
Mode of delivery [n (%)]			0.76
Vaginal delivery	94/135 (70)	94/135 (70)	
Operative vaginal delivery	12/135 (9)	15/135 (11)	
Cesarean section	29/135 (21)	26/135 (19)	
Blood loss (ml) (SD)			
Vaginal delivery	363 (267)	345 (202)	0.60
Caesarean section	564 (256)	570 (288)	0.94
Birth weight (g) (SD)	3550 (568)	3527 (615)	0.75
Length (cm) (SD)	50.3 (4.4)	50.0 (2.5)	0.44
Ponderal index (kg/m^3) (SD)	28.4 (0.2)	28.2 (0.2)	0.48
Head circumference (cm) (SD)	35.5 (1.7)	35.0 (1.6)	0.01
Placenta weight (g) (SD)	666 (152)	673 (165)	0.74
APGAR score < 7 (%)			
1 min (%)	8/135 (5.9)	7/135 (5.2)	1.00
5 min (%)	2/135 (1.5)	2/135 (1.5)	1.00
10 min (%)	0/135 (0)	1/135 (0.8)	1.00
Umbilical artery pH [mean (SD)]	7.25 (0.10)	7.27 (0.10)	0.34
pH < 7.10 [n (%)]	4/74 (5.4)	3/85 (3.5)	0.71
Newborn sex [n (%)]			0.63
Male	70/135 (52)	65/135 (48)	
Female	65/135 (48)	70/135 (52)	
Weight [n (%)]			0.32
$\leq$2500 g	8/135 (5.9)	8/135 (5.9)	
2501–4500 g	125/135 (92.6)	120/135 (88.9)	
$>$4500 g	2/135 (1.5)	7/135 (5.2)	

Labor onset was defined as at least 3 cm cervical opening and regular contractions. Blood loss was estimated by the midwife or the doctor in charge of the delivery. To account for multiple comparisons, we consider *P* value = 0.01 as significant.

placenta weight between the groups (Table 3). However, neonatal head circumference was larger in the metformin group compared with the placebo group.

Compliance and per protocol analyses

Among the 270 pregnancies (three were lost to follow-up, because of spontaneous abortions), 201 (74.7%) reported good compliance, 15 women (5.5%) reported acceptable compliance, and 54 (19.8%) reported poor compliance or were dropouts. No difference in compliance was observed between the metformin and placebo groups (data not

shown). In the per protocol analyses, we included those 216 women who had good and acceptable compliance. We found fewer preterm deliveries in the metformin group compared with the placebo group (*P* = 0.03) (Table 4). Otherwise, we found no differences in baseline data or other primary or secondary endpoint data between the study groups.

Post hoc analyses

Subgroups stratified according to body mass index (BMI) of 30 kg/m^2 or lower and BMI higher than 30 kg/m^2 showed no difference between the study groups (Supple-

TABLE 4. Subgroup analyses: per protocol analyses of primary outcome measures

	Metformin [n (%)]	Placebo [n (%)]	Risk difference (%)	95% CI	*P* value
Preeclampsia	9/108 (8.3)	5/108 (4.6)	3.7%	−2.8–10.3	0.27
Preterm delivery ($<37 + 0$)[a]	3/108 (2.8)	11/108 (10.2)	−7.4%	0.9–13.9	0.03
New GDM	18/100 (18.0)	18/98 (18.4)	−0.2%	−10.9–10.5	0.97
Composite primary endpoints	28/108 (25.9)	30/108 (27.8)	−1.9%	−14.0–10.0	0.76

Included in these analyses were 216 women classified as having good and acceptable compliance. Gestational age for the preterm deliveries in the metformin group were gestational wk 35, 36, and 36. Gestational age for the preterm deliveries in the placebo group were gestational wk 30, 31, 32, 32, 34, 34, 34, 35, 36, 36, and 36. New GDM was diagnosed after inclusion in the study. To account for multiple comparisons, we use *P* value = 0.01 as significant.

[a] If we use Fisher's exact test, the *P* value is 0.05.

mental Table 1a, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Analyses of subgroups stratified according to meeting NIH criteria and meeting only Rotterdam criteria showed fewer preterm deliveries in the metformin group among those who met NIH criteria ($P = 0.04$) (Supplemental Table 1b).

Maternal and newborn diagnoses in pregnancy, delivery, and postpartum and fetal congenital malformations according to treatment groups are shown in Supplemental Table 2.

Major adverse events

In the metformin group, we observed one postpartum pulmonary embolism, one postpartum circulatory shock, one peripartum cardiomyopathy and one sudden infant death. In the placebo group, we observed three spontaneous abortions, ileus in one patient with former gastric bypass operation, and one perinatal infant death caused by serious asphyxia (Supplemental Table 2).

Minor adverse events

Diarrhea was commoner in the metformin group throughout the entire pregnancy compared with the placebo group. Bloating was more often experienced before wk 19 in the metformin group compared with the placebo group. Nausea, vomiting, abdominal discomfort, and metal taste in the mouth were similar in both groups (Supplemental Table 3).

Discussion

Contrary to our hypothesis and data from our pilot study (20), the results of this randomized controlled trial (RCT) do not support the theory that metformin reduces pregnancy complications in PCOS. Our findings differ from reports on the benefits of metformin treatment during pregnancy, given that, without exception, all of them cite a positive effect (5, 9, 14–20, 23). These reports are, however, based on study designs that are prone to different sorts of bias, including our own pilot study where we found higher prevalence of serious pregnancy complications in the placebo group. Well-conducted RCTs such as ours are the cornerstone for medical practice. Moreover, our data are consistent with a large multicenter RCT on metformin *vs.* insulin treatment of a GDM population where no benefits of metformin were seen on preeclampsia and preterm delivery (24). Our study has parallels to the trial of Legro *et al.* (25). After many years of use in fertility treatment, based on smaller studies, the RTC showed that metformin was inferior to traditional ovulation stimulation.

It is noteworthy that metformin, an insulin-sensitizing drug, did not reduce the prevalence of GDM. We cannot explain this except that active diet and lifestyle management in both groups may have reduced the effect of metformin on glucose homeostasis. Alternatively, the pathogenetic mechanism for GDM differs from the mechanism of type 2 diabetes mellitus in the nonpregnant state, metformin affecting only the latter.

At inclusion, no limitations were set on BMI or PCOS phenotype. The study population mirrors the clinical heterogeneity of PCOS regarding both disease phenotype and degree of obesity. Data on nonpregnant PCOS indicate that metformin reduces insulin resistance and hyperandrogenism more in nonobese compared with obese women (13). This was the rationale for performing stratified, *post hoc* analyses according to a BMI below and above 30 kg/m^2. We also analyzed our data according to PCOS diagnostic criteria. The use of the Rotterdam criteria widens the diagnostic definition for PCOS compared with the NIH criteria, which is more conservative and strict. Preterm birth was less frequent among those who met NIH criteria in the metformin group. Nevertheless, this finding should be interpreted with caution because of multiple testing and *post hoc* analyses. It is theoretically possible that some subgroups of PCOS women could benefit from metformin in pregnancy, but from the present study, we cannot conclude that any particular subgroup would benefit from metformin treatment. Per protocol analyses shows a tendency toward fewer preterm births in the metformin group, but also here is a need to interpret with caution because of subgroup analysis and multiple comparisons. Only a new RCT can clarify this question.

The uniform results by planned and *post hoc* analysis of our study make it plausible that results may be generalized to other populations, for example to a more obese population. However, 95% of the participants were Caucasians, which is an obvious limitation of the study. Sixteen women participated twice. The results are not changed if we analyze only the first participation, *i.e.* 257 pregnancies.

Our study did not address the possible effect of metformin on early pregnancy loss or the benefits of continuing metformin after verified pregnancy. To answer these questions, a study designed to initiate metformin/placebo before conception and continued through pregnancy should be conducted. The prevalence of pregnancy complications in our study was lower than in previous reports on PCOS. This can probably be explained by differences in baseline characteristics of the study populations, because previous smaller studies might have included PCOS women who were more affected by the condition. Another explanation could be that all participants had tight and thorough pregnancy follow-up and had diet and lifestyle

intervention, which has been reported to be beneficial (26). This could theoretically mask a small effect of metformin. But, not having lifestyle intervention would have been unethical.

The results of previous reports indicating a beneficial effect of metformin in PCOS pregnancies have led to widespread use of the drug. Our study of metformin treatment from the first trimester to delivery does not show any benefit of the drug on study endpoints and speaks against this practice.

Acknowledgments

References

1. **Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, 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

2. **Franks S** 1995 Polycystic ovary syndrome. N Engl J Med 333:853–861

3. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R** 1998 Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 83:3078–3082

4. **Consensus** 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19:41–47

5. **Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS** 2006 A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 12:673–683

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

7. **de Vries MJ, Dekker GA, 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

8. **Gjønnaess 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

9. **Glueck CJ, Goldenberg N, Wang P, Loftspring M, 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

10. **Carlsen SM, Romundstad P, Jacobsen G** 2005 Early second trimester hyperandrogenemia and subsequent preeclampsia: a prospective study. Acta Obstet Gynecol Scand 84:117–121

11. **Serin IS, Kula M, Baþbuð M, Unlühizarci K, Güçer S, Tayyar M** 2001 Androgen levels of preeclamptic patients in the third trimester of pregnancy and six weeks after delivery. Acta Obstet Gynecol Scand 80:1009–1013

12. **Steier JA, Ulstein M, Myking OL** 2002 Human chorionic gonadotropin and testosterone in normal and preeclamptic pregnancies in relation to fetal sex. Obstet Gynecol 100:552–556

13. **Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH** 2009 Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev CD003053

14. **Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P** 2001 Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. Fertil Steril 75:46–52

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

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

17. **Glueck CJ, Pranikoff J, Aregawi D, Wang P** 2008 Prevention of gestational diabetes by metformin plus diet in patients with polycystic ovary syndrome. Fertil Steril 89:625–634

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

19. **Nawaz FH, Khalid R, Naru T, Rizvi J** 2008 Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? J Obstet Gynaecol Res 34:832–837

20. **Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM** 2004 Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. Hum Reprod 19:1734–1740

21. **Expert Committee on Diagnosis and Classification of Diabetes Mellitus** 1998 Report of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1998(Suppl 1):S5–S19

22. **WHO Consultation Group** 1998 Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation Group. Geneva: World Health Organization

23. **Begum MR, Khanam NN, Quadir E, Ferdous J, Begum MS, Khan F, Begum A** 2009 Prevention of gestational diabetes mellitus by continuing metformin therapy throughout pregnancy in women with polycystic ovary syndrome. J Obstet Gynaecol Res 35:282–286

24. **Rowan JA, Hague WM, Gao W, Battin MR, Moore MP** 2008 Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 358:2003–2015

25. **Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert PC, Myers ER** 2007 Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 356:551–566

26. **Khoury J, Henriksen T, Christophersen B, Tonstad S** 2005 Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. Am J Obstet Gynecol 193:1292–1301