ORIGINAL ARTICLE

Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus

Argyro Syngelaki, Ph.D., Kypros H. Nicolaides, M.D., Jyoti Balani, M.D., Steve Hyer, M.D., Ranjit Akolekar, M.D., Reena Kotecha, M.D., Alice Pastides, M.D., and Hassan Shehata, M.D.

ABSTRACT

BACKGROUND

Obesity is associated with an increased risk of adverse pregnancy outcomes. Lifestyle-intervention studies have not shown improved outcomes. Metformin improves insulin sensitivity and in pregnant patients with gestational diabetes it leads to less weight gain than occurs in those who do not take metformin.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned pregnant women without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 35 to receive metformin, at a dose of 3.0 g per day, or placebo (225 women in each group) from 12 to 18 weeks of gestation until delivery. The BMI was calculated at the time of study entry (12 to 18 weeks of gestation). The primary outcome was a reduction in the median neonatal birth-weight z score by 0.3 SD (equivalent to a 50% reduction, from 20% to 10%, in the incidence of large-for-gestational-age neonates). Secondary outcomes included maternal gestational weight gain and the incidence of gestational diabetes and of preeclampsia, as well as the incidence of adverse neonatal outcomes. Randomization was performed with the use of computer-generated random numbers. The analysis was performed according to the intention-to-treat principle.

RESULTS

A total of 50 women withdrew consent during the trial, which left 202 women in the metformin group and 198 in the placebo group. There was no significant between-group difference in the median neonatal birth-weight z score (0.05 in the metformin group [interquartile range, −0.71 to 0.92] and 0.17 in the placebo group [interquartile range, −0.62 to 0.89], P=0.66). The median maternal gestational weight gain was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2], P<0.001), as was the incidence of preeclampsia (3.0% vs. 11.3%; odds ratio, 0.24; 95% confidence interval, 0.10 to 0.61; P=0.001). The incidence of side effects was higher in the metformin group than in the placebo group. There were no significant between-group differences in the incidence of gestational diabetes, large-for-gestational-age neonates, or adverse neonatal outcomes.

CONCLUSIONS

Among women without diabetes who had a BMI of more than 35, the antenatal administration of metformin reduced maternal weight gain but not neonatal birth weight. (Funded by the Fetal Medicine Foundation; ClinicalTrials.gov number, NCT01273584; EudraCT number, 2008-005892-83.)

From the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital (A.S., K.H.N., R.A., R.K., A.P.), and the Departments of Endocrinology (J.B., S.H.) and Maternal Medicine (H.S.), Epsom and St. Helier University Hospitals NHS Trust, London, and the Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, Kent (R.A.) — all in the United Kingdom. Address reprint requests to Dr. Shehata at the Department of Maternal Medicine, Epsom and St. Helier University Hospitals NHS Trust, London SM5 1AA, United Kingdom, or at hassan.shehata@nhs.net.

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The prevalence of obesity is increasing both in developed countries and in developing countries, and obesity is considered to be a global pandemic.[1] An estimated one fifth of pregnant women in the United Kingdom and one third of those in the United States are obese.[2,3] Obesity during pregnancy is associated with an increased risk of adverse short-term and long-term consequences for both mother and baby.[4-11] Attempts at reducing the incidence of pregnancy complications associated with obesity have focused on dietary and lifestyle interventions, but these have generally been unsuccessful.[12-17]

An alternative strategy is the use of metformin, which reduces insulin resistance. Metformin has been used extensively in the treatment of gestational diabetes mellitus,[18] and there has been no evidence of an increase in the incidence of birth defects associated with its use.[19] Hyperglycemia and increased insulin resistance occur with obesity[20] and may explain the association between obesity and fetal macrosomia, as well as other pregnancy complications.[21] Studies involving women with gestational diabetes mellitus have shown that metformin reduces gestational weight gain.[18,22] The Metformin in Obese Nondiabetic Pregnant Women (MOP) trial was designed to test the hypothesis that metformin, as compared with placebo, would be associated with a lower median neonatal birth-weight z score when administered to pregnant women without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 35.

Methods

Trial Design and Participants

In this study, we randomly assigned women without diabetes who had a BMI of more than 35 and were at 12 to 18 weeks of gestation with a singleton fetus to receive metformin or placebo. Participants were from three National Health Service (NHS) maternity hospitals in the United Kingdom (King's College Hospital, London; Medway Maritime Hospital, Kent; and Epsom and St. Helier University Hospitals NHS Trust, London). In these hospitals, all women receiving pregnancy care are offered an ultrasonographic examination at 11 to 13 weeks of gestation as part of combined screening for trisomy 21. Pregnancy dating was based on the measurement of the fetal crown–rump length at that scan. The BMI was calculated at the time of study entry (12 to 18 weeks of gestation). The demographic characteristics of the mothers and the medical history were recorded in a database.

Exclusion criteria were a maternal age of less than 18 years; a major fetal defect observed on the scan performed at 11 to 13 weeks of gestation; a history of gestational diabetes mellitus; kidney, liver, or heart failure; a serious medical condition; hyperemesis gravidarum; treatment with metformin at the time of screening; known sensitivity to metformin; and miscarriage before randomization. Potential trial participants were given written information about the trial; they then had at least 24 hours to consider participation. All the women who agreed to participate in the trial provided written informed consent.

Ethical approval for the study was obtained from the London–Surrey Borders Research Ethics committee, and clinical trial authorization was obtained from the Medicines and Healthcare Products Regulatory Agency. The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

Two of the authors wrote the first draft of the manuscript, and all the authors contributed to its revision and made the decision to submit the manuscript for publication. Study funding was provided by the Fetal Medicine Foundation, which had no role in the study design, the collection, analysis, or interpretation of the data, or the writing of the report. Quality control of screening and verification of adherence to protocols at the various centers were performed on a regular basis by the trial coordinators.

Randomization and Study-Group Assignments

Eligible women were randomly assigned, in a 1:1 ratio, with the use of computer-generated random numbers, to receive either metformin or placebo. In the random-sequence generation there were no restrictions, such as block size or stratification according to study site. The appearance, size, weight, and taste of the placebo tablets were identical to those of the metformin tablets; both were purchased at full cost from University College London Hospitals NHS Foundation Trust.

The women in each group were prescribed metformin or placebo on their first visit after randomization. All the women received standard-

ized personal advice on healthy eating, with an emphasis on low-glycemic-index foods, and were encouraged to exercise for 30 minutes each day.

The metformin or placebo was given with meals; metformin was initiated at a daily dose of 1.0 g in week 1, and the dose was increased by 0.5 g per week to a maximum dose of 3.0 g in week 5. Women with serious side effects while taking the full dose were asked to continue taking the maximum tolerated dose. The study regimen was stopped if fetal growth restriction — defined by an estimated fetal weight lower than the fifth percentile and abnormal results of fetal Doppler studies — was detected.

FOLLOW-UP VISITS

Follow-up visits were scheduled at intervals of 4 to 6 weeks for prescription of metformin or placebo and for maternal assessment, including measurement of weight and blood pressure and urinalysis for proteins and ketones. We assessed adherence to taking metformin or placebo by counting the tablets returned by the patients at each visit; if during a given visit a patient forgot to return the tablets, we relied on verbal report and on the results of previous and subsequent visits. Adherence was considered to be good if the total number of tablets consumed was at least 50% of the total number prescribed and poor if it was less than 50%.

All the women underwent an 75-g oral glucose-tolerance test (OGTT) at 28 weeks of gestation; metformin or placebo was stopped for 1 week before the date of the test. Women with abnormal results on the OGTT (i.e., results that met the World Health Organization 1999[23] criteria for gestational diabetes mellitus) were advised to continue the assigned study regimen as before and to commence home glucose monitoring. If target blood-glucose values were not achieved, insulin was added to their existing regimen. Women with normal OGTT results continued with the study regimen as before.

The clinical data of the participants were recorded in the study database at each visit. Details regarding delivery and neonatal outcomes were added as soon as they became available.

OUTCOME MEASURES

The primary outcome measure was the median neonatal birth-weight z score (difference between observed and expected birth weight, with adjustment for gestational age, divided by the fitted standard deviation). The expected birth weight, corrected for gestational age, was derived from our population of phenotypically normal neonates born alive at 24 weeks of gestation or later.[24]

Maternal secondary outcome measures included gestational weight gain, which was defined as the difference in maternal weight between the day of randomization and the last antenatal visit, gestational diabetes mellitus, preeclampsia,[25] pregnancy-induced hypertension,[25] delivery by cesarean section, and postpartum hemorrhage, which was defined as blood loss of 1 liter or more. Key secondary outcomes for the fetus or neonate included death before 24 weeks of gestation, stillbirth at 24 weeks of gestation or later, preterm birth before 37 weeks of gestation, status of being large for gestational age (birth weight >90th percentile, with adjustment for gestational age),[24] birth trauma (shoulder dystocia, or brachial plexus injury or fracture), an Apgar score of less than 7 at 5 minutes, admission to a level 2 or 3 neonatal unit, hypoglycemia (plasma glucose levels <46.8 mg per deciliter [2.6 mmol per liter] on two occasions ≥30 minutes apart), hyperbilirubinemia requiring phototherapy, and respiratory distress, which was defined by the need for more than 4 hours of respiratory support or supplemental oxygen.

ADVERSE EVENTS

Patients were advised to contact their local investigator if any adverse events occurred. The nature, time of onset, and severity of the event, the treatment needed, and any relation to the assigned study regimen were recorded. All serious adverse events were reported to the sponsor.

STATISTICAL ANALYSIS

The sample-size estimation was based on our data from 72,013 singleton pregnancies for which routine screening was performed for trisomies at 11 to 13 weeks of gestation. At that screening visit, the maternal weight and height were measured and the BMI was calculated. In that large population, the neonatal birth weight was normally distributed, with a median (±SD) of 3381±563 g.

In the subgroup of pregnancies in which the mother's BMI was 35 or less (67,354 women), the median neonatal birth weight was 3351 g, and the prevalence of large-for-gestational-age neonates was 10%. In the subgroup of pregnan-

cies in which the mother's BMI was more than 35 (4659 women), the median neonatal birth weight was 3516 g, and the prevalence of large-for-gestational-age neonates was 20%. Therefore, the median birth weight in neonates whose mothers had a BMI of more than 35 was 0.3 SD (165÷563) higher than in those whose mothers had a BMI of 35 or less.

Since metformin is associated with less gestational weight gain[18,22] and since birth weight is related to both maternal BMI and gestational weight gain,[10,26] we hypothesized that the use of metformin in women with a BMI of more than 35 might result in a reduction in the mean neonatal birth weight by 0.3 SD — down to the value observed in neonates born to women with a BMI of 35 or less. We estimated that 400 patients would need to undergo randomization to give the study 80% power to detect such a reduction at a 5% significance level; after allowing for an expected withdrawal of 20%, we calculated that we would need to recruit 450 patients. The analysis was performed according to the intention-to-treat principle.

Baseline data for the mothers in the two study groups were summarized with the use of medians and interquartile ranges. Comparisons between groups were performed with the use of the Mann–Whitney U test. Univariate comparisons of dichotomous data were performed with the use of the chi-square test or Fisher's exact test.

RESULTS

STUDY POPULATION

The study period was from October 2010 through June 2015 at Epsom and St. Helier University Hospitals, from June 2013 through June 2015 at King's College Hospital, and from September 2013 through June 2015 at Medway Maritime Hospital. In all the hospitals, there was a 5-month gap in recruitment because of problems with the manufacture of the drugs. At Epsom and St. Helier University Hospitals, several periods of interruption occurred because of problems with personnel.

A total of 1071 women without diabetes who had a BMI of more than 35 and a singleton pregnancy were assessed for eligibility, but 227 were excluded (Fig. 1). Of the 844 eligible women, 450 (53.3%) agreed to participate in the study. After randomization, 50 women (23 women in the metformin group and 27 in the placebo group) withdrew consent. Withdrawal of consent occurred within 10 days after enrollment in 42 of the 50 cases (84%) and at 14 to 49 days in the remaining 8 cases.

The maternal characteristics and obstetrical history of the 202 participants in the metformin group and the 198 participants in the placebo group are shown in Table 1. There were no significant between-group differences in the characteristics at baseline apart from maternal age, which was higher in the metformin group than in the placebo group.

OUTCOME MEASURES

There were no significant differences between the metformin group and the placebo group in the median neonatal birth-weight z score, the incidence of large-for-gestational-age neonates, or the incidence of adverse fetal or neonatal outcomes (Table 2). The median gestational weight gain in the mother and the incidence of preeclampsia were lower in the metformin group than in the placebo group, but there were no significant between-group differences in the other secondary outcomes (Table 2; and Tables S1 through S4 and Fig. S1 in the Supplementary Appendix, available at NEJM.org). In the total cohort of participants, there was a significant association between maternal gestational weight gain and the incidence of preeclampsia ($r=0.17$, $P=0.001$).

ADVERSE EVENTS

There was no significant between-group difference in the incidence of serious adverse events, but the incidence of side effects was higher in the metformin group than in the placebo group (Table 3, and Table S5 in the Supplementary Appendix). In response to side effects, 17.6% of the women stopped taking their tablets, 41.8% reduced the dose, and 40.6% continued with the full dose; there were no significant between-group differences with regard to these decisions. In seven patients (two patients in the metformin group and five in the placebo group), the study regimen was stopped because of fetal growth restriction, as evidenced by an estimated fetal weight below the 5th percentile and abnormal fetal Doppler studies.

ADHERENCE

The maximum tolerated daily dose of metformin or placebo was 3.0 g in 254 of the 400

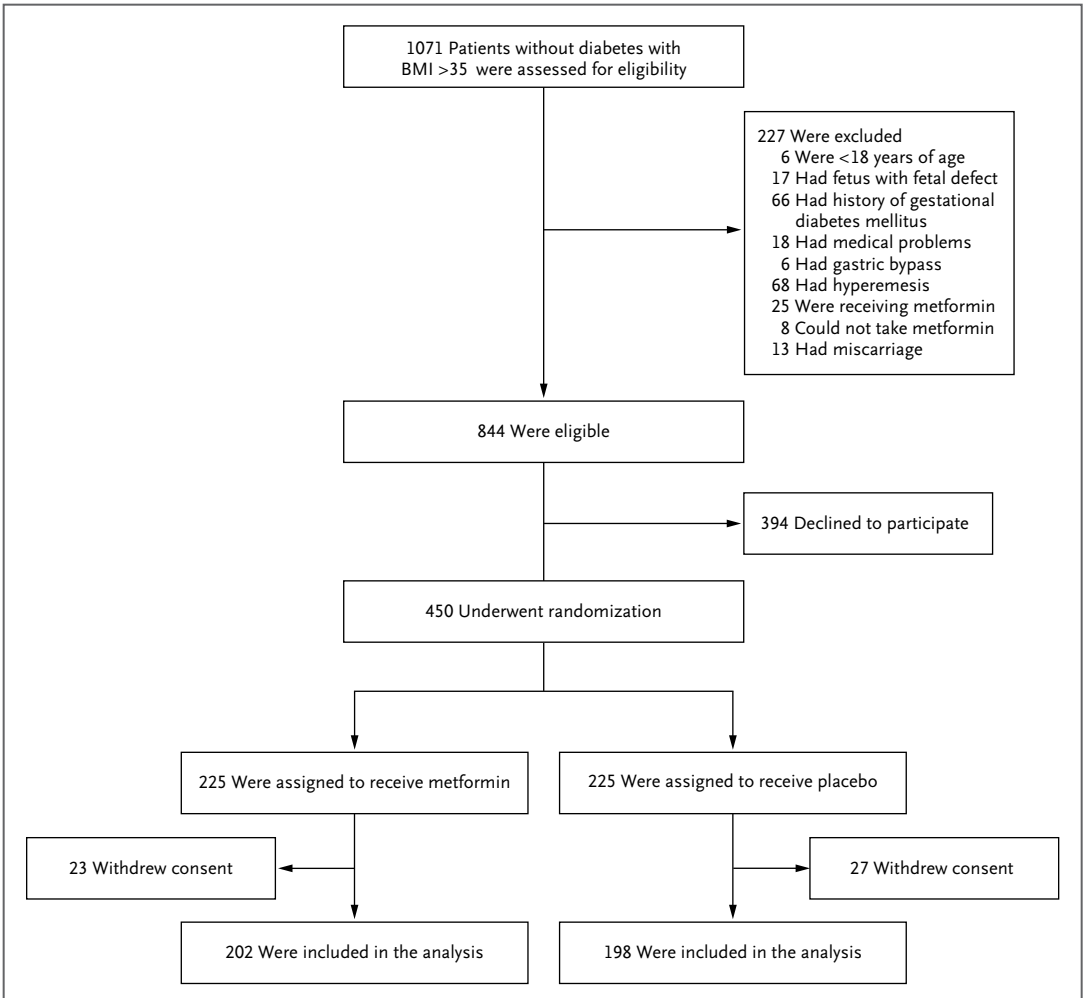

Figure 1. Screening, Randomization, and Analysis Populations.
The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

women (63.5%), 2.0 or 2.5 g in 57 women (14.2%), and less than 2 g in 89 women (22.2%); the number of women taking each dose was used as the denominator in calculating the rate of adherence (Table S6 in the Supplementary Appendix). Adherence was good in 318 women (79.5%) and poor in 82 (20.5%). The prevalence of good adherence was directly related to the final maximum tolerated dose of medication; the prevalence was 93.5% among women taking the full dose of 3.0 g and only 53.3% among those who were taking less than 2.0 g of the drug. There were no significant between-group differences in the degree of adherence.

DISCUSSION

Our trial showed that in pregnant women without diabetes who had a BMI of more than 35, the daily administration of metformin from 12 to 18 weeks of gestation until delivery did not reduce the median neonatal birth-weight z score or the incidence of large-for-gestational-age neonates. However, metformin was associated with less maternal gestational weight gain and a lower incidence of preeclampsia than were seen with placebo. There was no significant difference between the groups in the incidence of other pregnancy complications or of adverse fetal or neonatal outcomes.

Side effects, including nausea and vomiting, diarrhea, and headache, were as expected during gestation, but the incidence of side effects was significantly higher in the metformin group than in the placebo group. However, among the women with side effects, there were no significant between-group differences with regard to the decision of whether to continue with the full dose, reduce the dose, or stop the study regimen. Regardless of side effects, adherence to the study regimen was good (≥50% of tablets taken) in nearly 80% of the women and did not differ significantly between the two groups. The rate of adherence was considerably higher among women taking the full dose of 3.0 g per day than among those taking less than 2.0 g per day, which suggests that adherence was not driven by the presence or absence of side effects but by the motivation of the patients to adhere to the demands of the study.

The major strengths of our trial include the racially heterogeneous nature of the participating women, who had moderate-to-severe obesity and were selected from a screened population of women receiving routine pregnancy care. In addition, a high percentage of eligible women agreed to participate and they also had a high rate of adherence to the study regimen.

The study has certain limitations. It was not adequately powered for the secondary outcomes. In a screening study involving 120,492 women with singleton pregnancies in our population, the incidence of preeclampsia was 2.2%,[9] and in the subgroup of 7152 women (5.9%) with a BMI of more than 35, the incidence was 5.5%. For a randomized trial to have 80% power to detect a reduction in the incidence of preeclampsia from 5.5% to the observed 3.0% in the metformin group, at a 5% significance level, 2050 patients would need to be recruited.

We found that, among obese women, less gestational weight gain was associated with a lower prevalence of preeclampsia. This finding is compatible with the results of several previous studies that showed that the prevalence of preeclampsia increased with both increasing prepregnancy BMI and increasing gestational weight gain.[9,10,26-28]

Most previous studies that have investigated the effect of metformin on pregnancy outcome have involved women with the polycystic ovary syndrome.[29-32] In four randomized, controlled trials, metformin or placebo was given from 5 to 6 weeks of gestation until delivery. One trial involving 40 women who received metformin at

Table 1. Maternal Characteristics and Obstetrical History, According to Study Group.*

Characteristic	Metformin (N=202)	Placebo (N=198)
Median maternal age (IQR) — yr	32.9 (27.3–36.2)	30.8 (26.6–34.4)
Median maternal weight (IQR) — kg†	104.7 (95.7–116.2)	105.4 (97.0–115.5)
Median maternal height (IQR) — cm	165 (160–168)	165 (160–169)
Median body-mass index (IQR)‡	38.6 (36.5–41.5)	38.4 (36.3–41.9)
Median gestational age at randomization (IQR) — wk	15.1 (13.7–17.0)	14.9 (13.6–17.3)
Race or ethnic group — no. (%)§		
White	142 (70.3)	128 (64.6)
Black	50 (24.8)	55 (27.8)
South Asian	7 (3.5)	12 (6.1)
East Asian	1 (0.5)	0
Mixed	2 (1.0)	3 (1.5)
Medical history — no. (%)		
Chronic hypertension	13 (6.4)	17 (8.6)
Polycystic ovary syndrome	26 (12.9)	18 (9.1)
Cigarette smoking	15 (7.4)	21 (10.6)
Conception — no. (%)		
Spontaneous	197 (97.5)	194 (98.0)
Ovulation induction	2 (1.0)	3 (1.5)
In vitro fertilization	3 (1.5)	1 (0.5)
Parity — no. (%)		
Nulliparous	55 (27.2)	68 (34.3)
Parous with previous preeclampsia	14 (6.9)	13 (6.6)
Parous with previous large-for-gestational-age neonate	39 (19.3)	31 (15.7)

* Comparison between groups was performed with the use of the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. There were no significant ($P<0.05$) between-group differences in any of the characteristics listed here except for maternal age, which was higher in the metformin group than in the placebo group ($P=0.02$). IQR denotes interquartile range.

† The pregnancy weight was measured at the time of study entry (12 to 18 weeks of gestation).

‡ The body-mass index (the weight in kilograms divided by the square of the height in meters) was calculated at the time of study entry (12 to 18 weeks of gestation).

§ Race or ethnic group was self-reported.

Table 2. Pregnancy Outcomes, According to Study Group.*

Outcome	Metformin (N=202)	Placebo (N=198)	Odds Ratio (95% CI)	P Value
Primary outcome				
Median birth-weight z score (IQR)	0.05 (–0.71 to 0.92)	0.17 (–0.62 to 0.89)	—	0.66
Fetal or neonatal outcomes				
Miscarriage — no. (%)	0	3 (1.5)	—	0.12
Stillbirth — no. (%)	1 (0.5)	2 (1.0)	0.49 (0.04 to 5.42)	0.62
Neonatal death — no. (%)	0	1 (0.5)	—	0.49
Live birth — no. (%)	201 (99.5)	192 (97.0)	6.28 (0.78 to 52.66)	0.12
Delivery at <37 weeks of gestation — no./total no. (%)	13/202 (6.4)	21/195 (10.8)	0.57 (0.28 to 1.17)	0.12
Median birth-weight percentile (IQR)	51.8 (23.9 to 82.1)	56.6 (26.8 to 81.4)	—	0.66
Large for gestational age — no./total no. (%)†	34/202 (16.8)	30/195 (15.4)	1.11 (0.65 to 1.90)	0.79
Birth trauma — no. (%)	3/202 (1.5)	3/195 (1.5)	0.96 (0.19 to 4.84)	1.00
Apgar score at 5 min <7 — no. (%)	1/202 (0.5)	3/195 (1.5)	0.32 (0.03 to 3.09)	0.36
Admission to NICU — no./total no. (%)	11/202 (5.4)	14/195 (7.2)	0.74 (0.33 to 1.68)	0.47
Hypoglycemia — no./total no. (%)	9/202 (4.5)	11/195 (5.7)	0.78 (0.32 to 1.93)	0.58
Hyperbilirubinemia — no./total no. (%)	11/202 (5.4)	15/195 (7.7)	0.69 (0.31 to 1.54)	0.36
Respiratory distress syndrome — no./total no. (%)	9/202 (4.5)	13/195 (6.7)	0.65 (0.27 to 1.56)	0.33
Maternal outcomes				
Median weight gain (IQR) — kg	4.6 (1.3 to 7.2)	6.3 (2.9 to 9.2)	—	<0.001
Gestational diabetes mellitus — no./total no. (%)	25/202 (12.4)	22/195 (11.3)	1.11 (0.60 to 2.04)	0.74
Preeclampsia — no./total no. (%)	6/202 (3.0)	22/195 (11.3)	0.24 (0.10 to 0.61)	0.001
Pregnancy-induced hypertension — no./total no. (%)	13/202 (6.4)	13/195 (6.7)	0.96 (0.43 to 2.13)	0.93
Delivery by cesarean section — no./total no. (%)	80/202 (39.6)	82/195 (42.1)	0.93 (0.62 to 1.38)	0.79
Postpartum hemorrhage — no./total no. (%)	19/202 (9.4)	16/195 (8.2)	1.16 (0.58 to 2.33)	0.67

* The percentages for delivery before 37 weeks of gestation, birth trauma, Apgar score less than 7 at 5 minutes, admission to the neonatal intensive care unit (NICU), hypoglycemia, hyperbilirubinemia, and the respiratory distress syndrome and all secondary maternal outcomes were calculated after the exclusion of three patients with miscarriage in the placebo group. Data on median birth-weight z score and percentile were missing for three neonates in the placebo group. The comparison between groups was performed with the use of the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. In view of multiple comparisons, a P value of less than 0.0025, rather than less than 0.05, was considered to indicate statistical significance. CI denotes confidence interval.

† Large-for-gestational-age status was defined by a neonatal weight that was higher than the 90th percentile.

a dose of 1.7 g per day or placebo showed that metformin had no significant effect on neonatal birth weight or on the incidence of preeclampsia or maternal gestational diabetes mellitus.[29] These results were confirmed by a larger study involving 273 women and a higher dose of metformin of 2.0 g per day; that study showed that women who received the drug had significantly less maternal gestational weight gain than did those who received placebo but that metformin was not associated with a significantly lower median neonatal birth weight or incidence of preeclampsia, gestational diabetes mellitus, or preterm birth.[30] In contrast, a trial involving 40 women showed that metformin at a dose of 1.7 g per day was associated with a significantly lower rate of preeclampsia than the rate among women who received placebo.[31] Another study involving 40 women showed that metformin at a dose of 850 mg per day, as compared with placebo, had no significant effect on the incidence of gestational diabetes mellitus.[32]

One recent randomized, controlled trial, the Effect of Metformin on Maternal and Fetal Out-

Table 3. Serious Adverse Events among Trial Participants.*

Category and Event	Metformin (N = 202)	Placebo (N = 198)
Fetal death		
Miscarriage	0	3
Stillbirth	1	2
Fetal defect		
Arachnoid cyst, diagnosed prenatally at 32 wk	1	0
Moderate unilateral hydronephrosis, diagnosed prenatally at 34 wk	0	1
Transposition of the great arteries, diagnosed postnatally	1	0
Trisomy 21, diagnosed postnatally	1	0
Fetal disease		
Congenital hyperinsulinism	1	0
Fetal anemia due to Rh hemolytic disease, with delivery at 33 wk	1	0
Maternal disease		
Admission for acute fatty liver at 32 wk	1	0
Admission for chest pain postnatally	0	1
Admission for dehydration at 27 wk	1	0
Admission for fibula and tibia fracture at 33 wk	1	0
Admission for gestational asthma at 30 wk	1	0
Admission for headache and neurologic symptoms at 16 wk	0	1
Admission for numbness in both legs at 32 wk	0	1
Admission for pancreatitis at 33 wk	1	0
Admission for psychosis at 37 wk	0	1
Admission for pyelonephritis at 34 wk	0	1
Admission for tachycardia at 33 wk	1	0
Scar dehiscence in woman with four previous cesarean sections, at 28 wk	0	1
Preeclampsia or fetal growth restriction		
Admission for preeclampsia and subsequent preterm delivery	1	6
Admission for preeclampsia and subsequent full-term delivery	0	2
Admission for gestational hypertension and subsequent full-term delivery	0	1
Admission for fetal growth restriction and subsequent preterm delivery	1	2
Preterm birth		
Admission for preterm prelabor amniorrhexis	4	6
Admission for cervical cerclage for short cervix	1	1
Admission for preterm labor, with subsequent full-term delivery	1	1
Spontaneous early preterm birth	1	2
Vaginal bleeding		
Admission for vaginal bleeding prepartum	0	5

* None of these serious adverse events was considered by the investigators to be associated with metformin or placebo.

comes in Obese Pregnant Women (EMPOWaR) trial, examined the effect of metformin at a dose of 2.5 g per day, administered from 16 to 18 weeks of gestation to delivery, in 449 white women without diabetes who had a BMI of more than 30.[33] That study showed no significant differences between the metformin group and the placebo group in the median birth weight, ma-

ternal gestational weight gain, the rate of preeclampsia, or the rate of adverse perinatal events. In our study, all racial groups were included so that the results would potentially be applicable to the general population. We also used a BMI cutoff point of 35 rather than 30 because the incidence of adverse pregnancy outcomes is much higher when the mother's BMI is more than 35 than when it is more than 30; the cutoff point of 35 enabled the study to have adequate power with a smaller sample size.[10] Finally, we used a 3.0-g dose of metformin, as compared with the 2.5-g dose used in the EMPOWaR trial, to avoid potential criticisms, in the event of no effect, that the dose was inadequate, particularly in women with a very high BMI.

The EMPOWaR trial had 15 participating centers; our study had only 3 participating centers, which allowed closer supervision of the study and direct contact with most patients by a small group of researchers. This difference may have contributed to the higher rate of eligible women who agreed to participate and remain in the trial (47% [400 of 844 women] in our study vs. 13% [443 of 3329 women] in the EMPOWaR trial). Similarly, adherence to the study regimen was higher in our study, in which it was estimated that nearly 80% of women consumed at least 50% of the total number of tablets prescribed. In the EMPOWaR trial, women were considered to have adhered to the study regimen if they took a minimum of one tablet of 500 g for at least 29% of the days between randomization and delivery; only 67% of women fulfilled these criteria.

The failure of the EMPOWaR trial to show that the use of metformin was associated with less gestational weight gain and a lower incidence of preeclampsia than were seen with placebo — findings that were observed in our study — may be the consequence of lower adherence to an adequate dose of medication. In our study, nearly 66% of the women in the metformin group took a minimum dose of 2.5 g for at least 50% of the days between randomization and delivery. In the EMPOWaR trial, 2.5 g of metformin was taken for only 38% of the days between randomization and delivery in the group of patients receiving this dose, but the proportion of patients who were in this dose subgroup was not specified.

In conclusion, in pregnant obese women without diabetes mellitus, prophylactic therapy with a daily dose of 3.0 g of metformin from 12 to 18 weeks of gestation until delivery was associated with less maternal gestational weight gain than that observed with placebo but not with a lower median neonatal birth weight.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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