ORIGINAL ARTICLE

Metformin versus Insulin for the Treatment of Gestational Diabetes

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ABSTRACT

BACKGROUND

Metformin is a logical treatment for women with gestational diabetes mellitus, but randomized trials to assess the efficacy and safety of its use for this condition are lacking.

METHODS

We randomly assigned 751 women with gestational diabetes mellitus at 20 to 33 weeks of gestation to open treatment with metformin (with supplemental insulin if required) or insulin. The primary outcome was a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score less than 7, or prematurity. The trial was designed to rule out a 33% increase (from 30% to 40%) in this composite outcome in infants of women treated with metformin as compared with those treated with insulin. Secondary outcomes included neonatal anthropometric measurements, maternal glycemic control, maternal hypertensive complications, postpartum glucose tolerance, and acceptability of treatment.

RESULTS

Of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. The rate of the primary composite outcome was 32.0% in the group assigned to metformin and 32.2% in the insulin group (relative risk, 1.00; 95% confidence interval, 0.90 to 1.10). More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%, P<0.001). The rates of other secondary outcomes did not differ significantly between the groups. There were no serious adverse events associated with the use of metformin.

CONCLUSIONS

In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment. (Australian New Zealand Clinical Trials Registry number, 12605000311651.)

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Gestational diabetes is a complication in about 5% of pregnancies, is increasing in prevalence, and is associated with complications to the pregnancy and a long-term risk of diabetes in both mother and offspring.[1-5] Intervention to change lifestyle and, if maternal hyperglycemia persists, treatment with additional insulin have been shown to improve perinatal outcomes.[6,7] Women who begin insulin therapy require education to ensure the safe administration of insulin. Use of insulin is also associated with hypoglycemia and weight gain. The use of safe and effective oral agents may offer advantages over insulin.

Oral metformin is a logical option for women with gestational diabetes mellitus. It improves insulin sensitivity, probably by activating AMP kinase, and is not associated with weight gain or hypoglycemia.[8,9] Reported outcomes of its use during pregnancy have been favorable[10-19] except for one small, retrospective cohort study[20] that showed increased rates of perinatal loss and preeclampsia as compared with insulin treatment. Metformin crosses the placenta and could affect fetal physiology directly.[21] Its use in pregnancy remains controversial; to our knowledge, only two small, randomized trials comparing metformin with insulin have been reported to date.[22,23]

We designed the Metformin in Gestational Diabetes Trial to rule out a 33% increase in a composite of perinatal complications in infants of women treated with metformin as compared with insulin. Our hypotheses were that perinatal outcomes would be similar for both treatments, that women would consider metformin a more acceptable treatment than insulin, and that metformin would improve markers of insulin sensitivity in the mother and baby.

Methods

Study Design

We conducted this randomized, open-label trial comparing metformin with insulin treatment in 10 New Zealand and Australian urban obstetrical hospitals. The ethics review boards at all sites approved the study, and the participants gave written informed consent. Details of the study design have been published elsewhere.[24] Dr. Rowan vouches for the integrity and completeness of the data.

Study Subjects

Women were eligible for inclusion if they were between 18 and 45 years of age, had received a diagnosis of gestational diabetes mellitus according to the criteria of the Australasian Diabetes in Pregnancy Society (ADIPS),[25] were pregnant with a single fetus between 20 and 33 weeks of gestation, met the hospital's usual criteria for starting insulin treatment, and, after lifestyle intervention consisting of advice about diet and exercise, had more than one capillary blood glucose measurement above 5.4 mmol per liter (97.2 mg per deciliter) after an overnight fast or more than one 2-hour postprandial blood glucose measurement above 6.7 mmol per liter (120.6 mg per deciliter). The exclusion criteria were a prepregnancy diagnosis of diabetes, a contraindication to metformin, a fetal anomaly, gestational hypertension, preeclampsia, fetal growth restriction, and ruptured membranes.

Randomization was performed with a block size of four and was stratified according to site and gestational age (from 20 weeks to 27 weeks 6 days, or from 28 weeks to 33 weeks 6 days). All sites agreed to aim for the capillary glucose levels recommended by the ADIPS[25] (level after an overnight fast, <5.5 mmol per liter [99 mg per deciliter]; 2-hour postprandial level, <7.0 mmol per liter [126 mg per deciliter]), although several sites aimed for lower levels.

The women obtained the prescribed medications from their local pharmacies. Metformin (Metomin in New Zealand [Pacific Pharmaceuticals] and Diaformin in Australia [Alphapharm and other nonspecified manufacturers]) was started at a dose of 500 mg once or twice daily with food and increased, typically over a period of 1 to 2 weeks, to meet glycemic targets up to a maximum daily dose of 2500 mg. If the targets were not achieved with metformin alone, insulin was added. Metformin was stopped if maternal contraindications (such as liver or renal impairment or sepsis) or fetal growth restriction developed. Insulin was prescribed according to usual practice.

Data Collection

Demographic and clinical data were recorded at enrollment. Blood samples were obtained after an overnight fast to assess baseline glycemia and to ensure that the results of renal- and liver-function tests did not preclude the use of metformin. Glu-

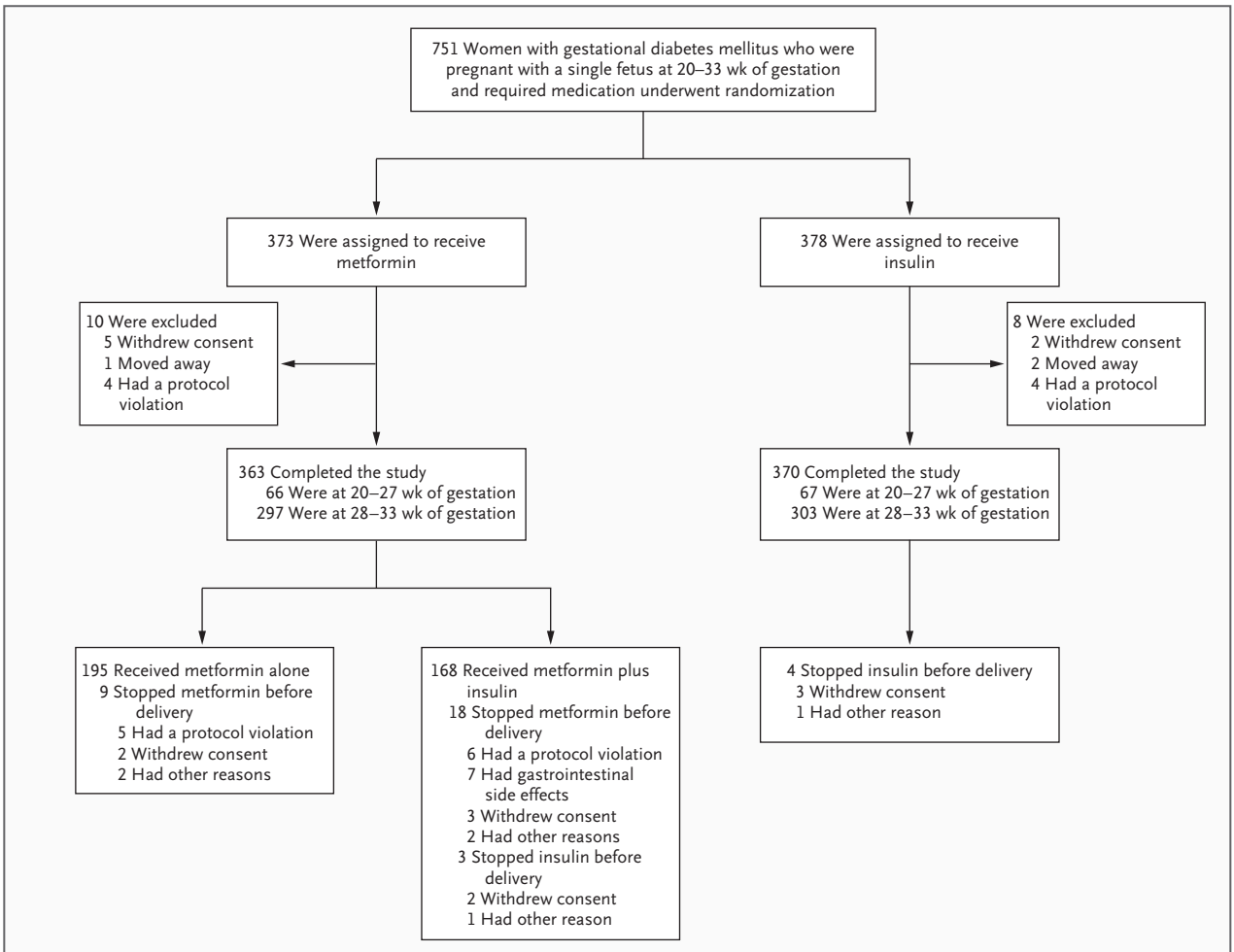

Figure 1. Enrollment of Subjects.

cose, glycated hemoglobin, and triglycerides were measured in local laboratories; glucose was measured in venous plasma by a hexokinase method, and glycated hemoglobin was measured by methods yielding results that were consistent with those of the Diabetes Control and Complications Trial. The women performed blood glucose measurements at home with the use of a MediSense meter; the results after an overnight fast and the 2-hour postprandial results were downloaded and transcribed into the database. At 36 to 37 weeks of gestation, venous plasma glucose was again measured after an overnight fast. At delivery, complications of pregnancy, the indication for delivery, the mode of delivery, and neonatal complications were recorded.

After the umbilical cord had been clamped, cord blood was collected in tubes containing EDTA and in plain tubes and sent for processing within 10 minutes after collection or stored on ice for processing within 90 minutes. After centrifugation, 1-ml aliquots were stored in a freezer at −80°C. Serum insulin concentration was measured in a single laboratory with the use of a Roche Diagnostics Elecsys 2010 automated analyzer and an Elecsys 1010/2010 insulin kit (no. 2017547). An equal volume of 25% polyethylene glycol-6000 was added to each sample to precipitate the antibodies before analysis. The coefficients of variation of insulin concentration were 1.8% at 1050 pmol per liter (175 mU per liter), 2.0% at 330 pmol per liter (55 mU per liter), and 4.8% at 38 pmol per liter (6 mU per liter).

STUDY OUTCOMES

The primary outcome was a composite of neonatal complications, with components chosen to reflect important adverse effects of fetal exposure to

maternal hyperglycemia that might be modified by treatment and directly influenced by the passage of metformin across the placenta.[24] The components of the composite outcome were neonatal hypoglycemia (two or more neonatal glucose values <2.6 mmol per liter [46.8 mg per deciliter]), respiratory distress (need for at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during the first 24 hours after delivery), need for phototherapy, birth trauma (injury to the baby at delivery, documented as mild if bruises or abrasions were present at birth but resolved before 6 weeks post partum; more serious injuries were also recorded), 5-minute Apgar score below 7, or premature birth (<37 weeks of gestation). The neonates were monitored for hypoglycemia by measuring blood glucose levels within 2 hours after birth and before each feeding until consecutive glucose values of 2.6 mmol per liter (46.8 mg per deciliter) or greater were achieved. Readings below 2.6 mmol per liter and below 1.6 mmol per liter (28.8 mg per deciliter) were documented, as was treatment for hypoglycemia.

Maternal hypertensive complications were diagnosed according to Australasian guidelines.[26] Birth-weight percentiles were calculated with the use of a customized calculator[27] that adjusts for sex and gestational age of the infant, as well as maternal height, weight in early pregnancy, ethnic group, and parity. Neonatal anthropometric measurements, including crown–heel length, crown–rump length, head circumference, chest circumference, abdominal circumference, mid-upper-arm circumference, triceps skin-fold thickness, and subscapular skin-fold thickness, were obtained within 48 hours after birth by trained personnel.[24]

Table 1. Maternal Characteristics at Baseline.*

Characteristic	Metformin Group (N=363)	Insulin Group (N=370)
Age — yr	33.5±5.4	33.0±5.1
Body-mass index†		
In early pregnancy‡	32.2±8.2	31.9±7.6
At enrollment	35.1±8.3	34.6±7.2
Length of gestation at enrollment — wk	30.2±3.3	30.1±3.2
Race or ethnic group — no. (%)§		
European or white	175 (48.2)	168 (45.4)
Polynesian¶	73 (20.1)	83 (22.4)
Indian	38 (10.5)	55 (14.9)
Chinese or Southeast Asian	49 (13.5)	37 (10.0)
Other or mixed	28 (7.7)	27 (7.3)
Tertiary education — no. (%)	161 (44.4)	162 (43.8)
Smoking during pregnancy — no. (%)	63 (17.4)	58 (15.7)
Chronic hypertension — no. (%)	31 (8.5)	27 (7.3)
Nulliparous — no. (%)‖	115 (31.7)	118 (31.9)
Obstetrical history — no. (%)		
≥3 Pregnancy terminations or miscarriages	84 (23.1)	62 (16.8)**
Gestational diabetes mellitus	94 (25.9)	81 (21.9)
Preeclampsia	30 (8.3)	25 (6.8)
Gestational hypertension	28 (7.7)	32 (8.6)
Infant with birth weight >4000 g	83 (22.9)	79 (21.4)
Cesarean delivery	83 (22.9)	86 (23.2)
Delivery at <37 wk	45 (12.4)	45 (12.2)
Infant with congenital anomaly	15 (4.1)	12 (3.2)

Table 1. (Continued.)

Characteristic	Metformin Group (N=363)	Insulin Group (N=370)
Family history — no. (%)††		
Diabetes	162 (44.6)	181 (48.9)
Hypertension	144 (39.7)	142 (38.4)
Preeclampsia	33 (9.1)	35 (9.5)
Blood pressure at enrollment — mm Hg		
Systolic	113.1±13.1	113.4±12.7
Diastolic	68.8±9.3	68.1±9.1
Results of preintervention 75-g oral glucose-tolerance test — mg/dl‡‡		
Plasma glucose level after an overnight fast	102.6±21.6	102.6±19.8
2-Hr postprandial plasma glucose level	174.6±37.8	169.2±37.8
Plasma glucose level at enrollment after an overnight fast	93.6±18.0	95.4±19.8
Glycated hemoglobin — %§§	5.7±0.6	5.8±0.7

* Plus–minus values are means ±SD.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The body-mass index values in early pregnancy (i.e., before 20 weeks of gestation) are based on 281 women in the metformin group and 304 in the insulin group.
§ Race and ethnic group were self-reported.
¶ The Polynesian subjects included 137 Pacific Islanders and 19 Maori.
‖ Nulliparous women had had no previous pregnancy beyond 20 weeks.
** P=0.03; all other differences were not significant (P≥0.05).
†† A family history was recorded if the condition was present in a first-degree or second-degree relative.
‡‡ In women who did not have a 75-g oral glucose-tolerance test, the investigator verified the presence of gestational diabetes mellitus by the presence of a high glucose level in a random sample or a sample taken 1 hour after a 50-g glucose load, and lifestyle intervention and capillary glucose monitoring were initiated before the women were considered for enrollment in the trial. The values for fasting plasma glucose are based on 321 women in the metformin group and 330 in the insulin group, the values for 2-hour postprandial plasma glucose are based on 320 women in the metformin group and 319 in the insulin group, and the values for fasting plasma glucose at enrollment are based on 324 women in the metformin group and 294 in the insulin group. To convert values for glucose to millimoles per liter, divide by 18.
§§ The values are based on 345 women in the metformin group and 319 in the insulin group.

A questionnaire was administered to the mothers in the first postpartum week to assess acceptability of the treatment.

Adverse events were reported to the data and safety monitoring committee. Side effects of medication and complications of pregnancy were documented at clinic visits, and the investigators were informed of hospitalizations. Congenital anomalies and events that were fatal, life-threatening, associated with serious disability or incapacity, required prolonged hospitalization (apart from hospitalization related to expected pregnancy events), or required a major intervention to prevent another serious outcome were classified as serious adverse events. Other measures of neonatal complications were admission to a level 2 or level 3 neonatal intensive care unit, duration of stay in the neonatal intensive care unit, and diagnosis at discharge from the hospital. In cases in which fetal pH was measured in blood from the scalp or umbilical cord, the lowest value was recorded. The secondary outcome measures were maternal and neonatal body composition, maternal glycemic control, maternal hypertensive complications, maternal glucose tolerance at 6 to 8 weeks post partum, and acceptability of treatment.

STATISTICAL ANALYSIS

The pretrial estimate of the frequency of the primary outcome was 30% (on the basis of local data from women who had been treated with insulin). The anticipated rates for each component were 14% for hypoglycemia, 5% for respiratory distress, 5% for phototherapy, 1.5% for birth trauma, less than 1% for Apgar scores below 7, and 15% for preterm delivery. The infants could meet one or more of

Table 2. Primary Outcome and Additional Neonatal Complications.*

Outcome	Metformin Group (N=363)	Insulin Group (N=370)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary composite outcome	116 (32.0)	119 (32.2)	1.00 (0.90–1.10)	0.95
Recurrent blood glucose level <46.8 mg/dl†	55 (15.2)	69 (18.6)	0.96 (0.90–1.02)	0.21
Any blood glucose level <28.8 mg/dl	12 (3.3)	30 (8.1)	0.95 (0.92–0.98)	0.008
Respiratory distress‡	12 (3.3)	16 (4.3)	0.99 (0.96–1.02)	0.47
Transient tachypnea	7 (1.9)	8 (2.2)		
Respiratory distress syndrome	4 (1.1)	5 (1.4)		
Sepsis	1 (0.3)	5 (1.4)		
Pulmonary hypertension	0	2 (0.5)		
Phototherapy	29 (8.0)	31 (8.4)	0.99 (0.95–1.04)	0.85
Birth trauma§	16 (4.4)	17 (4.6)	1.00 (0.97–1.03)	0.90
Mild	16 (4.4)	15 (4.1)		
Moderate or severe	0	2 (0.5)		
5-Min Apgar score <7¶	3 (0.8)	1 (0.3)	1.01 (0.99–1.02)	0.37
Preterm birth (<37 wk of gestation)	44 (12.1)	28 (7.6)	1.06 (1.00–1.10)	0.04
Iatrogenic (indicated)	18 (5.0)	13 (3.5)	1.02 (0.98–1.05)	0.33
Spontaneous	26 (7.2)	15 (4.1)	1.03 (1.00–1.07)	0.07
Additional neonatal complications				
Admission to level 2 or 3 neonatal intensive care unit	68 (18.7)	78 (21.1)	0.97 (0.90–1.04)	0.43
>24-Hr stay in neonatal intensive care unit	46 (12.7)	45 (12.2)	1.01 (0.95–1.06)	0.83
	mean ±SD			
pH of umbilical-cord or scalp blood‖	7.27±0.07	7.26±0.07		0.32

* Treatment included supplemental feeding for 129 infants (35.5%) in the metformin group and 145 (39.2%) in the insulin group (P=0.31), nasogastric feeding for 9 infants (2.5%) in the metformin group and 14 (3.8%) in the insulin group (P=0.31), and intravenous dextrose for 25 infants (6.9%) in the metformin group and 22 (5.9%) in the insulin group (P=0.60). Induction of labor was performed in 196 women (54.0%) in the metformin group and 208 (56.2%) in the insulin group (P=0.55), cesarean section in 131 women (36.1%) in the metformin group and 142 (38.4%) in the insulin group (P=0.52), and emergency cesarean section in 55 women (15.2%) in the metformin group and 63 (17.0%) in the insulin group (P=0.49). Shoulder dystocia occurred in 6 deliveries (1.7%) in the metformin group and 11 (3.0%) in the insulin group (P=0.33).

† To convert values for glucose to millimoles per liter, divide by 18.

‡ Nine infants in each group were treated with continuous positive airway pressure. Five infants in the insulin group required intermittent positive-pressure ventilation (one of these infants subsequently received a diagnosis of tetralogy of Fallot).

§ Moderate or severe birth trauma included Erb's palsy, which resolved by 6 weeks of age in one infant, and a severe brachial plexus injury in another.

¶ All these infants had 5-minute Apgar scores of 6. In the metformin group, one infant had facial bruising and one preterm infant was admitted to the neonatal intensive care unit to establish feeding. Delivery was complicated by shoulder dystocia in one infant in the insulin group, who was admitted to the neonatal intensive care unit for observation.

‖ The values are based on 94 infants in the metformin group and 101 in the insulin group.

the criteria. The primary aim of the study was to rule out a clinically significant increase (from 30% to 40%) in the metformin group. Two-tailed calculations were used to rule out a significant difference in either direction. For 80% power and a 5% significance level, 375 subjects were required in each group.

The data were summarized as frequencies or percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables, depending on the distribution. Differences between the treatment groups were compared by the chi-square or Fisher's exact test for categorical variables and a

two-sample t-test or Mann–Whitney test for continuous variables. In addition to comparisons between the randomly assigned groups, data from women in the metformin group who were treated with metformin alone and those who had supplemental insulin were analyzed separately, with recognition that these were not randomized subgroups. Analyses were performed with SAS software, version 9.1 for Windows. Relative risks are reported with 95% confidence intervals.

Two interim analyses were conducted and reviewed by the data and safety monitoring committee. P values were adjusted by the Peto–Haybittle method. The investigators were to be informed if a difference in the primary outcome between treatment groups of three or more standard deviations was detected.

RESULTS

STUDY SUBJECTS

Enrollment of women for the study was completed between October 2002 and November 2006 (Fig. 1). Of the 751 women enrolled, 6 underwent randomization twice as a result of investigator errors; the errors were immediately recognized, and the first randomized treatment was assigned. Data after randomization were not available for 10 women in the metformin group and 8 in the insulin group, who therefore could not be included in the analysis. The analyses included the remaining 363 women in the metformin group and the 370 in the insulin group and were performed according to the intention-to-treat principle.

Supplemental insulin was required in 168 women (46.3%) in the metformin group. Metformin treatment was stopped in 27 women (7.4%) before delivery (Fig. 1). Treatment was stopped in 11 of these women in accordance with the trial protocol (9 women had obstetrical complications, 1 had sepsis, and 1 had worsening abnormal liver-function test results); treatment was stopped in 7 women (1.9%) because of gastrointestinal side effects; 5 women chose to stop metformin; and 4 women were advised to stop by other health professionals who were not involved in the trial. Metformin doses were reduced because of gastrointestinal side effects in 32 women (8.8%); all but 1 of these women were able to maintain a dose of at least 1000 mg per day.

The baseline characteristics of the two groups were similar (Table 1). The median daily dose of metformin was 2500 mg (interquartile range, 1750 to 2500). For women who required supplemental insulin, the median maximum daily dose of insulin was 42 units (interquartile range, 22 to 81), which was lower than the maximum daily dose in those assigned to insulin (50 units; interquartile range, 30 to 90) (P=0.002). Supplemental insulin was started at a median of 20.4 days (interquartile range, 12.4 to 27.5) after random assignment to metformin.

STUDY OUTCOMES

The primary outcome — a composite of neonatal complications — did not differ significantly between groups (32.0% in the metformin group and 32.2% in the insulin group, P=0.95) (Table 2). Of the outcomes included in the composite, severe hypoglycemia (glucose level <1.6 mmol per liter) was less common in the metformin group (P=0.008), but preterm birth (before 37 weeks of gestation) was more common in the metformin group (P=0.04) (Table 2). There was one delivery before 32 weeks of gestation in each treatment group. In the insulin group, delivery was due to an intrauterine fetal death at 29 weeks of gestation, the only perinatal loss in the study. This mother had been recruited at 20 weeks of gestation with a glycated hemoglobin value of 10.2%; at postmortem examination, the fetus had the Budd–Chiari syndrome. In an analysis according to indication for preterm birth, the frequency of iatrogenic preterm births was similar in both treatment groups, but there was a trend toward more spontaneous preterm births (spontaneous labor or preterm ruptured membranes) in the metformin group (Table 2). There was a statistically significant but clinically small difference in the mean gestational age at delivery between the metformin group (38.3 weeks) and the insulin group (38.5 weeks, P=0.02).

SECONDARY OUTCOMES AND ADDITIONAL MEASURES OF NEONATAL COMPLICATIONS

The secondary outcomes are summarized in Table 3. There were no significant differences between the groups in neonatal anthropometric measures or measurements of umbilical-cord serum insulin concentrations. Although the overall mean maternal 2-hour postprandial glucose levels were slightly lower in the metformin group, these values did not differ significantly between the groups in the 2 weeks before delivery (Table 3), a finding

Table 3. Secondary Outcomes and Additional Measurements.*

Variable	Metformin Group (N=363)	Insulin Group (N=370)	P Value
Neonatal			
Gestational age at birth — wk	38.3±1.4	38.5±1.3	0.02
Birth weight — g	3372±572	3413±569	0.33
Birth-weight percentile	54.6±30.1	54.3±31	0.91
Birth weight <10th percentile — no. (%)	26 (7.2)	36 (9.7)	0.21
Birth weight >90th percentile — no. (%)	70 (19.3)	69 (18.6)	0.83
Head circumference — cm	34.8±1.6	34.9±1.6	0.24
Crown–heel length — cm	50.3±2.8	50.3±2.4	0.87
Crown–rump length — cm†	33.4±2.7	33.6±2.6	0.46
Chest circumference — cm‡	33.9±2.3	34.1±2.5	0.33
Abdominal circumference — cm§	32.8±2.7	32.8±2.8	0.91
Mid-upper-arm circumference — cm§	11.2±1.3	11.1±1.4	0.51
Triceps skin-fold thickness — mm¶	5.2±1.6	5.1±1.2	0.30
Subscapular skin-fold thickness — mm‖	5.2±1.5	5.2±1.3	0.60
Ponderal index**	2.6±0.3	2.7±0.3	0.28
Umbilical-cord serum insulin concentration — pmol/liter††			0.18
Median	50.0	40.4	
Interquartile range	26.3–81.7	20.3–71.4	
Maternal‡‡			
Glycemic control from randomization until delivery			
Capillary glucose level after an overnight fast — mg/dl	93.6±10.8	91.8±12.6	0.24
2-Hr postprandial capillary glucose level — mg/dl	111.6±10.8	115.2±16.2	0.003
Glycemic control at 1 week after randomization			
Capillary glucose level after an overnight fast — mg/dl	100.8±16.2	99.0±18.0	0.31
Postprandial capillary glucose level — mg/dl	117.0±16.2	120.6±18.0	0.006
Glycemic control during the last 2 wk before delivery			
Capillary glucose level after an overnight fast — mg/dl	90.0±10.8	88.2±12.6	0.16
2-Hr postprandial capillary glucose — mg/dl	109.8±12.6	111.6±18.0	0.19
Glycated hemoglobin at wk 36–37 — %§§	5.6±0.5	5.7±0.6	0.25
Plasma glucose level at wk 36–37 after an overnight fast — mg/dl¶¶	81.0±10.8	79.2±12.6	0.10
Capillary glucose level 12 hr before delivery — mg/dl‖‖	97.2±10.8	95.4±16.2	0.35
Hypertensive complications — no. (%)***			
Gestational hypertension	14 (3.9)	23 (6.2)	0.14
Preeclampsia	20 (5.5)	26 (7.0)	0.40
Results of 75-g oral glucose-tolerance test at 6 to 8 wk post partum†††			
Fasting plasma glucose level — mg/dl	91.8±14.4	91.8±16.2	0.34
2-Hr postprandial plasma glucose level — mg/dl	115.2±43.2	115.2±41.4	0.87
Diabetes — no./total no. (%)	23/270 (8.5)	15/282 (5.3)	0.14
Impaired glucose level after an overnight fast — no./total no. (%)‡‡‡	13/270 (4.8)	13/282 (4.6)	0.91
Impaired glucose tolerance — no./total no. (%)§§§	30/270 (11.1)	41/282 (14.5)	0.23
Body-mass index	31.6±7.6	31.8±7.5	0.74

Table 3. (Continued.)

Variable	Metformin Group (N=363)	Insulin Group (N=370)	P Value
Weight change — kg			
Loss from enrollment to postpartum visit ¶¶¶	8.1±5.1	6.9±5.3	0.006
Gain from early pregnancy to enrollment‖‖‖	7.0±5.4	6.4±5.5	0.20
Gain from enrollment to 36 or 37 wk of gestation****	0.4±2.9	2.0±3.3	<0.001

* Plus–minus values are means ±SD.
† The values are based on 294 subjects in the metformin group and 297 in the insulin group.
‡ The values are based on 299 subjects in the metformin group and 301 in the insulin group.
§ The values are based on 298 subjects in the metformin group and 300 in the insulin group.
¶ The values are based on 292 subjects in the metformin group and 289 in the insulin group.
‖ The values are based on 291 subjects in the metformin group and 289 in the insulin group.
** The ponderal index is calculated as 100 times the birth weight in grams divided by the cube of the crown–heel length in centimeters.
†† There were 140 infants in the metformin group and 154 in the insulin group. To convert values for insulin to micrograms per liter, divide by 172.2. The P value was calculated by a t-test for the logarithm of umbilical-cord serum insulin.
‡‡ To convert values for glucose to millimoles per liter, divide by 18.
§§ The values are based on 280 subjects in the metformin group and 308 in the insulin group.
¶¶ The values are based on 279 subjects in the metformin group and 300 in the insulin group.
‖‖ The values are based on 311 subjects in the metformin group and 327 in the insulin group.
*** The diagnosis of hypertensive complications was made according to the Australasian Hypertension in Pregnancy Guidelines.[26]
††† Results are for 270 women in the metformin group and 282 in the insulin group, except for body-mass index (the weight in kilograms divided by the square of the height in meters), for which the results are for 301 women in the metformin group and 304 in the insulin group.
‡‡‡ Impaired glucose level after an overnight fast is defined as a plasma glucose level of 6.1 to 6.9 mmol per liter (110 to 124 mg per deciliter).
§§§ Impaired glucose tolerance is defined as a 2-hour postprandial plasma glucose level of 7.8 to 11.0 mmol per liter (140 to 198 mg per deciliter).
¶¶¶ The values are based on 301 subjects in the metformin group and 303 in the insulin group.
‖‖‖ The values are based on 281 subjects in the metformin group and 302 in the insulin group.
**** The values are based on 329 subjects in the metformin group and 300 in the insulin group. The weight gain from enrollment to 36 or 37 weeks of gestation in women taking metformin and supplemental insulin was 0.8±3.2 kg, as compared with 2.0±3.3 kg in those taking insulin alone (P<0.001).

suggesting that glucose targets were reached sooner in the metformin group. The rates of maternal hypertensive complications did not differ significantly between the two groups.

At 6 to 8 weeks post partum, 552 women (75.3%) underwent a 75-g oral glucose-tolerance test. In 62 of 270 women (23.0%) in the metformin group and 58 of 282 (20.6%) in the insulin group, glucose tolerance was impaired or diagnostic of diabetes. Women in the metformin group had greater weight loss between the time of enrollment and the postpartum visit and less weight gain between the time of enrollment and 36 weeks of gestation than did women in the insulin group (Table 3).

The results of the postpartum questionnaire assessing acceptability of treatment are shown in Table 4. Among women treated with metformin, 76.6% said they would choose metformin in a subsequent pregnancy, whereas 27.2% of women in the insulin group said they would choose insulin again (P<0.001). More women in the metformin group than in the insulin group said that taking medication was the easiest part of treatment (59.0% vs. 35.3%, P<0.001), and fewer women in the metformin group than in the insulin group said that taking medication was the hardest part of treatment (10.5% vs. 27.2%, P<0.001).

Serious adverse events affecting either the mother or the child are summarized in Table 5. There were no significant differences between the treatment groups, and none of the serious adverse events were considered by the data and safety monitoring committee to be treatment-related.

METFORMIN TREATMENT AND SUPPLEMENTAL INSULIN

As compared with women who were treated with metformin alone, women requiring supplemental insulin had a higher BMI and had higher baseline

Table 4. Results of Questionnaire on Acceptability of Treatment.*

Question	Metformin Group (N=334)	Insulin Group (N=331)	P Value
	no. (%)		
How often did you forget to take your medication?†			<0.001
Never or rarely	231 (69.4)	267 (80.7)	
1–3 times/wk	81 (24.3)	52 (15.7)	
4–6 times/wk	12 (3.6)	2 (0.6)	
>6 times/wk	9 (2.7)	10 (3.0)	
Which medication would you choose in another pregnancy?			<0.001
Metformin tablets	256 (76.6)	127 (38.4)	
Insulin injections	42 (12.6)	90 (27.2)	
Not sure	36 (10.8)	114 (34.4)	
In another pregnancy, if you were told you were likely to need insulin injections to control the sugar levels but could try metformin first, what would you prefer?			<0.001
Start with metformin and add insulin if needed	270 (80.8)	179 (54.1)	
Go straight to insulin injections	36 (10.8)	94 (28.4)	
Not sure	28 (8.4)	58 (17.5)	
Which part of your diabetes treatment was the easiest?			<0.001
Doing finger-prick tests	74 (22.2)	119 (36.0)	
Being careful with diet	63 (18.9)	95 (28.7)	
Taking medication	197 (59.0)	117 (35.3)	
Which part of your diabetes treatment was the hardest?			0.001
Doing finger-prick tests	123 (36.8)	91 (27.5)	
Being careful with diet	176 (52.7)	150 (45.3)	
Taking medication	35 (10.5)	90 (27.2)	

* Percentages may not sum to 100 because of rounding.
† One woman in the metformin group did not respond to this question.

glucose levels (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The rates of the primary outcome did not differ between women treated with metformin alone and those treated with supplemental insulin (29.7% and 34.5%, respectively; relative risk, 0.86; 95% confidence interval [CI], 0.64 to 1.16; P=0.33).

DISCUSSION

We found no significant increase in a composite measure of neonatal complications among women with gestational diabetes mellitus who were randomly assigned to metformin as compared with those who were assigned to insulin. Rates of neonatal hypoglycemia, one of the components of the composite end point, were similar in the two groups, but severe hypoglycemia (<1.6 mmol of glucose per liter [28.8 mg per deciliter]) occurred significantly less often in infants of women taking metformin. We did not see a reduction in the insulin concentration in umbilical-cord serum in the metformin group, but this finding should be interpreted with caution, since results were available for less than half of the participants.

Prematurity was included as part of the composite outcome. The rationale was that if metformin had any unanticipated adverse effect on fetal growth or well-being, there would be more iatrogenic preterm births. The frequency of preterm birth was higher in the metformin group than in the insulin group, but the difference was associated with a greater frequency of spontaneous (rather than iatrogenic) preterm births that could be due to chance or to an unrecognized effect of

Table 5. Adverse Events.

Event	Metformin Group (N=363)	Insulin Group (N=370)
	no. of subjects	
Serious maternal adverse events		
Infection requiring hospitalization	3	2
Antenatal	2	2
Postnatal	1	0
Surgery*	2	1
Antenatal	0	1
Postnatal	2	0
Pelvic arthropathy requiring opiate analgesia	1	1
Other events†	4	4
Serious fetal or neonatal adverse events		
Fetal death	0	1
Congenital anomalies‡	11	18
Cardiac	2	5
Genitourinary	4	2
Musculoskeletal	6	7
Other anomalies	0	6
Neonatal infection requiring hospitalization§	4	2
Other events¶	4	2
	no. (%)	
Important maternal adverse events‖		
Gastrointestinal events resulting in dose limiting	32 (8.8)	0
Gastrointestinal events resulting in treatment cessation	7 (1.9)	0
Maternal antepartum infection	44 (12.1)	38 (10.3)

* In the metformin group, one mother underwent surgery for cholecystectomy and one for placement of a right ureteric stent; in the insulin group, one mother had an appendectomy for appendicitis complicated by abscess.

† In the metformin group, there was one mother each with antepartum severe superficial thrombophlebitis, antepartum granulomatous mastitis, postpartum iatrogenic pulmonary edema, and postpartum anaphylactic reaction to anesthetic with stridor. In the insulin group, there were two mothers with severe preeclampsia (requiring prolonged hospitalization or care in an obstetrical intensive care unit) and one mother each with postpartum hemorrhage requiring transfusion and urinary incontinence.

‡ In the metformin group, two infants had small ventricular septal defects, three had hypospadias, one had hydronephrosis, two had talipes equinovarus, two had a dislocatable hip, and one had a bifid thumb. In the insulin group, two infants had ventricular septal defects, one had coarctation of the aorta, one had tetralogy of Fallot, one had an atrial septal defect with a minor cleft palate, one had choanal atresia, one had a ureterocele, one had hydronephrosis, one had hemifacial microsomia, three had talipes equinovarus, three had preauricular skin tags, and three had a dislocatable hip.

§ In the metformin group, one infant each had gastroenteritis, viral pneumonia, renal sepsis, and sepsis of unknown source. In the insulin group, one infant each had viral meningitis and cytomegalovirus infection.

¶ In the metformin group, one infant each had neonatal abstinence syndrome due to maternal use of opiates, stridor due to a short aryepiglottic fold, sensorineural hearing loss (probably due to a connexin mutation), and inguinal hernia requiring repair. In the insulin group, one infant each had trisomy 13 and hypoxic encephalopathy with Erb's palsy.

‖ Important adverse events were those leading to dose reduction or cessation of treatment or those occurring with a frequency of at least 5%.

metformin on the labor process. The increased rate of preterm birth was not associated with higher rates of other complications, probably because the difference between the two groups in mean gestational age at delivery was clinically insignificant. In a previous cohort of women with gestational diabetes mellitus who were treated with either insulin or glyburide, the rates of pre-

term delivery were 13% for the insulin group and 12% for the glyburide group, but the causes of preterm birth were not documented.[28]

In our study, 46.3% of women taking metformin required supplemental insulin. This proportion is likely to vary in other populations, depending on patient characteristics and target levels of glucose.

How do the effects of metformin in women with gestational diabetes mellitus compare with those reported for glyburide? In a randomized trial comparing glyburide and insulin in 404 women with gestational diabetes mellitus, glycemic control and pregnancy outcomes were similar between groups (although the trial was underpowered to address neonatal complications).[29] Subsequent experience with glyburide shows that approximately 20% of women change to insulin.[30,31] To our knowledge, there are no published trials comparing metformin with glyburide, and comparisons among available data are limited by differences in study populations and glycemic aims.

Although our study was not designed to compare the outcome of combined treatment with that of either treatment alone, the rate of neonatal complications did not differ significantly between women who required supplemental insulin and those who received metformin alone. Moreover, women receiving combined treatment required less insulin and gained less weight than those taking insulin alone.

Strengths of this trial are that it took place within routine clinical practice and included the spectrum of women with a diagnosis of gestational diabetes mellitus. A weakness is that treatment was open-label, since blinding was not considered practical or ethical. A methodologic limitation is that we used a superiority design to assess whether insulin was superior to metformin and have accepted rather than proved the null hypothesis (that there is no difference between treatments). Nonetheless, the 95% confidence interval for the relative risk of the composite measure of neonatal complications suggests that an increase in risk of more than 10% with metformin is implausible. In addition, a post hoc analysis using a noninferiority design and a proposed margin of 1.33 (33% change in complications) supports the conclusion that metformin is not inferior to insulin (relative risk, 1.00; 97.5% CI, 0.89 to 1.12). Finally, the composite outcome included outcomes of differing clinical significance.[32] However, data pertaining to the individual components of the composite measure serve to inform clinicians about several relevant effects of metformin.[24]

Clinicians may remain circumspect about using metformin until follow-up data for offspring are available. The offspring from this trial are being assessed at 2 years of age. Data at 18 months of age from 126 infants of women with polycystic ovarian syndrome who were treated with metformin have provided preliminary reassurance of a lack of effect on growth and on motor and social development.[33]

In conclusion, our findings suggest that metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with gestational diabetes mellitus who meet the usual criteria for starting insulin, and that metformin is more acceptable to women with gestational diabetes mellitus than is insulin. Further follow-up data are needed to establish long-term safety.

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APPENDIX

The following investigators participated in the Metformin in Gestational Diabetes Trial: steering committee members in Auckland, New Zealand — J. Rowan, T. Cundy, R. Elder, M. Battin; investigators in Adelaide, Australia, providing input to the steering committee — B. Hague, R. Haslam; site coordinators — A. Siegers (overall coordinator), M. Cropper, J. Rafferty, S. Coat (Australia national coordinator), C. Parker, A. Barry, G. Smith, T. Clarke, M. Cram, S. Hendon; data and safety monitoring committees, Green Lane (Auckland) and Flinders (Adelaide) Clinical Trial Centers — J. Harding, L. McCowan, R. Cutfield, W. Gao; umbilical-cord blood assays — P. Skidmore, EndoLab Christchurch Hospital; study sites and principal investigators (with numbers of subjects in parentheses): National Women's Hospital, Auckland, New Zealand — J. Rowan (282); Middlemore Hospital, Auckland, New Zealand — J. Rowan, J. Griffiths (114); Women's and Children's Hospital, Adelaide, Australia — W. Hague (181); King Edward Memorial Hospital, Perth, Australia — D. Graham, B. Walters (56); Royal Women's Hospital, Brisbane, Australia — K. Lust (29); Mater Misericordae Hospital, Brisbane, Australia — H.D. McIntyre (6); Christchurch Women's Hospital, Christchurch, New Zealand — P. Moore (29); Royal Women's Hospital, Melbourne, Australia — J. Oats, P. Wein (18); Wellington Hospital, Wellington, New Zealand — C. Eagleton (11); Blacktown Hospital, Sydney — M. McLean (7).

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