OBSTETRICS

Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial

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BACKGROUND: Gestational diabetes that is not properly controlled with diet has been commonly treated with insulin. In recent years, several studies have published that metformin can lead to, at least, similar obstetrical and perinatal outcomes as insulin. Nevertheless, not all clinical guidelines endorse its use, and clinical practice is heterogeneous.

OBJECTIVE: This study aimed to test whether metformin could achieve the same glycemic control as insulin and similar obstetrical and perinatal results, with a good safety profile, in women with gestational diabetes that is not properly controlled with lifestyle changes.

STUDY DESIGN: The metformin for gestational diabetes study was a multicenter, open-label, parallel arms, randomized clinical trial performed at 2 hospitals in Málaga (Spain), enrolling women with gestational diabetes who needed pharmacologic treatment. Women at the age of 18 to 45 years, in the second or third trimesters of pregnancy, were randomized to receive metformin or insulin (detemir or aspart). The main outcomes were (1) glycemic control (mean glycemia, preprandial and postprandial) and hypoglycemic episodes and (2) obstetrical and perinatal outcomes and complications (hypertensive disorders, type of labor, prematurity, macrosomia, large for gestational age, neonatal care unit admissions, respiratory distress syndrome, hypoglycemia, jaundice). Outcomes were analyzed on an intention-to-treat basis.

RESULTS: Between October 2016 and June 2019, 200 women were randomized, 100 to the insulin-treated group and 100 to the metformin-treated group. Mean fasting and postprandial glycemia did not differ between groups, but postprandial glycemia was significantly better after lunch or dinner in the metformin-treated-group. Hypoglycemic episodes were significantly more common in the insulin-treated group (55.9% vs 17.7% on metformin; odds ratio, 6.118; 95% confidence interval, 3.134−11.944; P=.000). Women treated with metformin gained less weight from the enrollment to the prepartum visit (36−37 gestational weeks) (1.35±3.21 vs 3.87±3.50 kg; P=.000). Labor inductions (45.7% [metformin] vs 62.5% [insulin]; odds ratio, 0.506; 95% confidence interval, 0.283−0.903; P=.029) and cesarean deliveries (27.6% [metformin] vs 52.6% [insulin]; odds ratio, 0.345; 95% confidence interval, 0.187−0.625; P=.001) were significantly lower in the metformin-treated group. Mean birthweight, macrosomia, and large for gestational age and babies' complications were not different between treatment groups. The lower cesarean delivery rate for women treated with metformin was not associated with macrosomia, large or small for gestational age, or other complications of pregnancy.

CONCLUSION: Metformin treatment was associated with a better postprandial glycemic control than insulin for some meals, a lower risk of hypoglycemic episodes, less maternal weight gain, and a low rate of failure as an isolated treatment. Most obstetrical and perinatal outcomes were similar between groups.

Key words: aspart insulin, cesarean deliveries, detemir insulin, gestational diabetes, hypoglycemia, metformin, oral antidiabetic drugs, pregnancy, randomized clinical trial, treatment satisfaction

Introduction

Women with gestational diabetes mellitus (GDM) need to achieve strict glycemic control to avoid pregnancy complications resulting from hyperglycemia. Insulin (INS) reduces these complications for both the mother and fetus.[1] Oral antidiabetic drugs are more easily managed by patients and non-specialized health teams, inexpensive, and accessible. Metformin (MET) use during pregnancy has been studied mainly for polycystic ovary syndrome[2] and GDM. It freely crosses the placenta into the fetus, but there is no evidence of an increase in congenital anomalies.[3] The metformin in gestational diabetes (MiG) trial[4,5] was the most relevant publication on the use of MET for GDM treatment. Afterward, several randomized clinical trials[6−15] and many reviews and meta-analyses have[16−18] or are trying[19] to shed light on this topic. MET lowered the risk of neonatal hypoglycemia, large for gestational age (LGA) babies, pregnancy-induced hypertension, and maternal weight gain.[16,18] The concern about its use is focused on the possible long-term metabolic programming of infants, because those exposed to MET in utero seem to experience accelerated postnatal growth, resulting in a higher body mass index or a higher risk of obesity by midchildhood.[20−22]

This study aimed to evaluate the efficacy and safety of MET compared with INS, regarding glycemic control and obstetrical and perinatal outcomes, in

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AJOG at a Glance

Why was this study conducted?

This study aimed to provide more knowledge about the efficacy and safety of metformin (MET) for the treatment of gestational diabetes mellitus (GDM).

Key findings

Compared with insulin, MET is effective and safe and achieves the same mean glycemia—with a slightly better postprandial glycemic control—with far less hypoglycemic events and much the same obstetrical and perinatal results.

What does this add to what is known?

This study supports the use of MET for GDM. It adds a systematic evaluation of hypoglycemic episodes.

pregnant women with GDM that is not controlled by lifestyle changes alone.

Materials and Methods

Trial design

The metformin for gestational diabetes study was a multicenter, open-label, parallel arms, randomized clinical trial, which enrolled women with GDM that needed pharmacologic treatment. It was performed at the hospitals Regional Universitario and Clínico Universitario Virgen de la Victoria (both in Málaga, Spain) and approved by the Research Ethics Committee and the Agencia Española de Medicamentos y Productos Sanitarios (European Union Clinical Trials Registry: EudraCT 2015-000361-31).

Patients

The inclusion criteria were singleton pregnancy, age of 18-45 years, and gestational age (GA) of 14 to 35 weeks. The exclusion criteria were language barrier, fasting glycemia at >120 mg/dL (6.7 mmol/L), and chronic gastrointestinal diseases.

Procedures

The diagnosis of GDM was established following local guidelines: selective screening occurred in the first (10 GA) and third trimesters (≥32 GA) and universal screening occurred between 24 and 28 GA. A 50-gram oral glucose screening (O'Sullivan test) was followed by a 100-gram oral glucose tolerance test (OGTT) using the National Diabetes Data Group criteria.[23] Isolated fasting glycemia at ≥100 mg/dL (5.6 mmol/L) was also considered as GDM.[24] Women were recommended lifestyle changes and self-blood glucose monitoring (SBGM) 4 times a day (fasting and 1-hour postprandial), using the Bayer Contour Next Glucose test strips, XT, or USB meters (Ascensia Diabetes Care, Basel, Switzerland); the GLUCOFACTS DELUXE software (Ascensia Diabetes Care) enabled the study team to download and confirm the patients glucose measurements. Targets for glycemic control were 70 to 95 mg/dL when fasting and ≤140 mg/dL 1 hour after meals. Failure of lifestyle changes alone to manage GDM was considered when 2 or more fasting glucose measurements were ≥95 mg/dL (5.3 mmol/L) per week and/or when 2 or more 1-hour postprandial measurements were ≥140 mg/dL (7.8 mmol/L) per week. When this occurred, women were recommended to initiate pharmacologic treatment and approached to participate in the study. Women who agreed to enroll in the trial were consented and then randomized (1:1) into the MET- or the INS-treated groups.

For the study, the following visits were intended: randomization, first follow-up visit (2 weeks after), additional visits every 2 to 4 weeks, prepartum (36−37 GA), and postpartum (8−12 weeks).

MET (Metformina Sandoz 850 mg, immediate-action form; Madrid, Spain) was started at 425 to 850 mg/d (breakfast, dinner, or both meals) and increased if needed (maximum of 2550 mg/d). For the INS-treated group, as required, detemir (Levemir, Novo Nordisk, Bagsvaerd, Denmark) at bedtime and/or aspart (NovoRapid, Novo Nordisk), 1 to 3 preprandial injections/d, were used. Detemir was started at 0.2 IU/kg (based on body weight at the time of randomization) and aspart at 0.1 IU/kg/meal. Women were trained in INS titration according to local protocols: if fasting glycemia was ≥95 mg/dL (≥2 days, consecutive or not), basal INS was increased 2 units from the next day on; if 1-hour postprandial glycemia was ≥140 mg/dL, prandial INS was increased 2 units. If proper glycemic control was not reached while on MET (with the same criteria than when we offered pharmacologic treatment), INS was added. INS adjustment is described in Appendix A.

Outcomes

The main outcomes of this study were glycemic control (mean glycemia and hypoglycemic events) and maternal and neonatal complications (hypertensive disorders of pregnancy, induced or spontaneous labor, preterm birth [spontaneous or iatrogenic], fetal growth [macrosomia, LGA, small for GA {SGA}], neonatal care unit [NCU] admission, respiratory distress syndrome, neonatal hypoglycemia, or jaundice requiring phototherapy).

Fasting and postprandial glycemia (from SBGM) and hypoglycemic events (symptoms reported since the last visit and events verified by SBGM in the previous week) were recorded at every visit. Hypoglycemia was divided into level 1 (<70 mg/dL [3.9 mmol/L]) and level 2 (<54 mg/dL [3.0 mmol/L])[25]; a third category (<60 mg/dL [3.3 mmol/L]) was also introduced. Hemoglobin A1c (HbA1c) was checked at randomization, at 35 to 37 GA, and at 8 to 12 weeks after delivery.

Hypertensive disorders of pregnancy (gestational hypertension, preeclampsia), delivery-related data (spontaneous or induced labor, operative vaginal, cesarean delivery), preterm birth (<37th GA), infant weight, Apgar scores, and perinatal complications (birth trauma, neonatal hypoglycemia [<40 mg/dL, <2.2 mmol/L], jaundice requiring phototherapy, respiratory distress syndrome,

NCU admissions) were also recorded. Babies were classified into macrosomia if they weighted >4.000 grams irrespective of GA, SGA if they were at the <10th percentile for GA at delivery and sex, or LGA if they were at the >90th percentile.[26] A combined variable named "any perinatal complication" (perinatal death, NCU admission, birth trauma, neonatal hypoglycemia, respiratory distress syndrome, or jaundice requiring phototherapy) was designed.

Other variables recorded were gestational weight gain, other treatment-related adverse effects (such as digestive complaints), fetal growth, congenital anomalies, and satisfaction with the treatment.

At inclusion, 35 to 37 GA, and 8 to 12 weeks after delivery, maternal blood samples were collected for glucose, creatinine, liver enzymes, HbA1c, lipids (triglycerides), thyroid stimulating hormone, and vitamin B12. At the postpartum visit, an OGTT (75 grams) was done.

Fetal growth was checked monthly (biparietal diameter, abdominal circumference, femur length, estimated fetal weight, estimated GA and percentile,[27] amniotic fluid index, and placental grading). Before childbirth, the modified biophysical profile assessment (ultrasounds for amniotic fluid index evaluation and cardiotocography) was performed according to our national guidelines.[28]

A structured survey about treatment acceptability, adapted from Rowan,[4] was completed in person at the last visit before delivery.

Statistical analysis

The sample size was calculated assuming a noninferiority margin of 25% and a variance of 0.3 for the macrosomia variable (from an expected 7.4% prevalence of macrosomia in our population).[29] Alpha error and statistical power were established at 0.05 and 80%, respectively. Assuming equal proportions for MET and INS, the sample size required would be 82 patients per group.

We performed an intention-to-treat analysis. Women on MET-treated group who required INS were analyzed as MET-treated group. Data were analyzed with IBM SPSS Statistics v19.0 (IBM Corp, Armonk, NY). Categorical variables are presented as frequencies, and continuous variables as means with standard deviation. Means were compared using parametric (Student *t*) or nonparametric (Mann Whitney *U*) tests after checking assumptions required. Proportions were compared with chi-square test. Several logistic regression models were done post hoc to confirm the association between relevant endpoints (cesarean deliveries, LGA), the group of treatment, and other variables of interest. Two-tailed tests were used, and statistical significance was established at $P<.05$.

Results

The trial profile is shown in the Figure. Between October 2016 and June 2019, 200 women were randomized into the INS (n=100) or MET (n=100) treatment groups. Basal characteristics were not different between groups (Table 1).

Primary findings

Glycemic control

There were no significant differences observed between groups for mean fasting or postprandial glycemia at 2 weeks after randomization and at 36 to 37 GA (Table 2). Greater postprandial glucose control was observed after some meals (lunch or dinner) in the MET-treated group vs the INS-treated group (2 weeks after inclusion: glycemia after lunch, 116.76±14.41 mg/dL [6.48±0.80 mmol/L] vs 123.78±15.68 mg/dL [6.87±0.87 mmol/L]; $P=.003$; after dinner, 121.44±13.87 mg/dL [6.74±0.77 mmol/L] vs 125.95±15.32 mg/dL [6.99±0.85 mmol/L]; $P=.041$). No differences were detected in HbA1c at 35 to 37 GA. Hypoglycemic events (1 or more) occurred more frequently in the INS-treated group than the MET-treated group (55.9% vs 17.7%; odds ratio [OR], 6.118; 95% confidence interval [CI], 3.134−11.944; $P=.000$); these episodes happened mostly after breakfast and in the late morning.

Obstetrical and perinatal outcomes (Tables 3 and 4)

Hypertensive disorders of pregnancy, preterm births, and GA at delivery were not significantly different between groups. Labor inductions (45.7% [MET] vs 62.5% [INS]; OR, 0.506; 95% CI, 0.283−0.903; $P=.029$) and cesarean deliveries (27.6% [MET] vs 52.6% [INS]; OR, 0.345; 95% CI, 0.187−0.625; $P=.001$) were significantly lower for the MET-treated group. The lower cesarean delivery rate for women treated with MET was not associated with macrosomia, LGA or SGA, or other complications of pregnancy. Birthweight, macrosomia, and LGA or SGA infants were not associated with the treatment (Table 3).

Detailed information about induction of labor, cesarean deliveries, and preterm births can be found in Appendix B.

No differences were observed between groups regarding perinatal outcomes (stay in NCU, respiratory distress syndrome, neonatal hypoglycemia, and jaundice requiring phototherapy) (Table 4).

Other findings

Women on MET put on less weight throughout pregnancy and from randomization to 36 to 37 GA (Table 3).

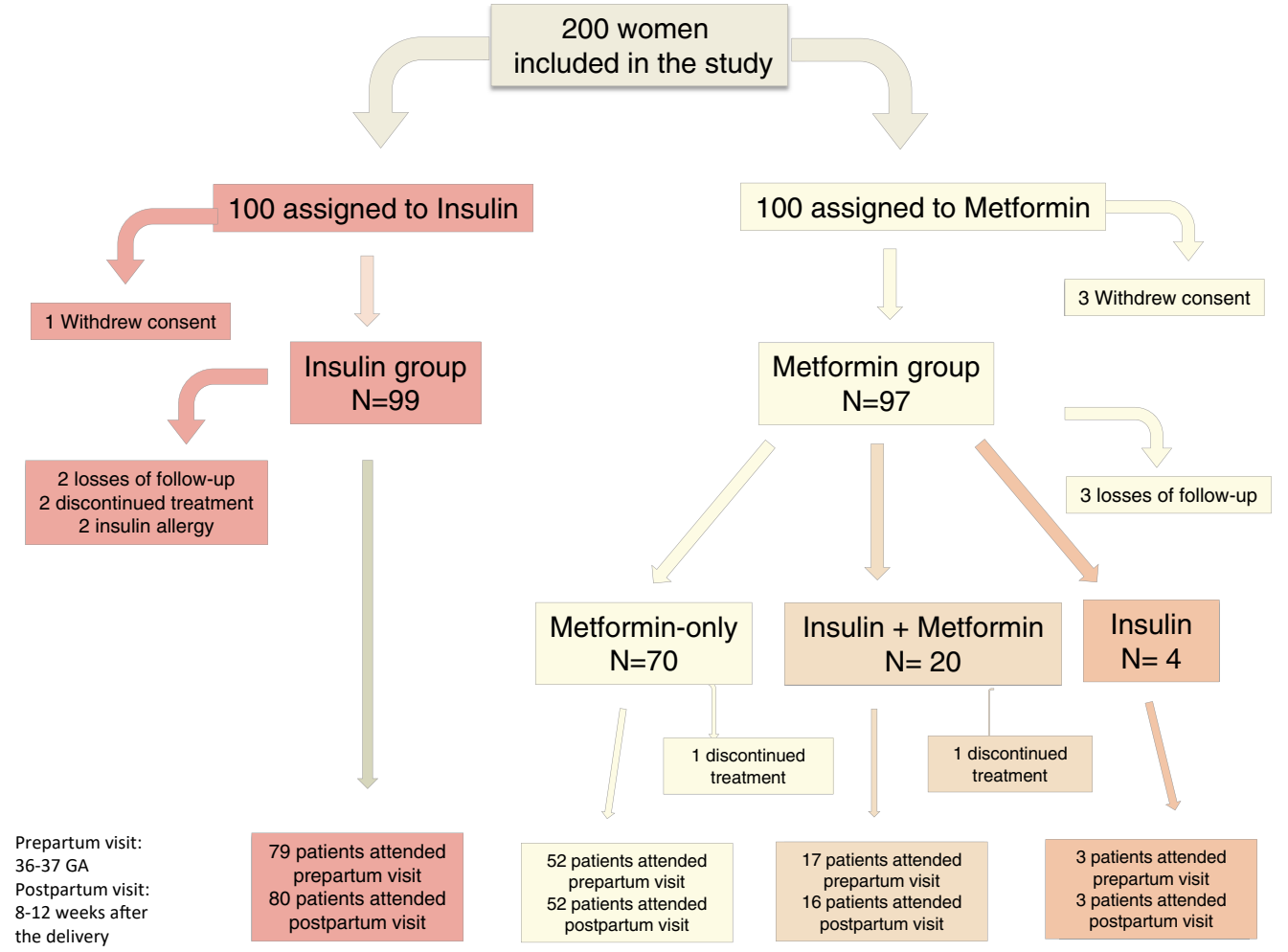
Patients in the MET-treated group reported more gastrointestinal complaints (63% [MET] vs 42% [INS]; $P=.006$). Two women experienced local reactions to detemir and were switched to glargine.

A total of 24 women from the MET-treated group required INS (MET+INS subgroup): 20 cases (21.3%) required adjunct INS because of insufficient glycemic control on MET alone, and 4 cases (4.2%) required INS owing to MET intolerance.

Excluding these 4 women from the MET-treated group for the analysis yielded the same obstetrical and perinatal outcomes (Appendix C).

Compared with women in the MET-only group, women in the MET+INS group had experienced GDM—and also had required INS more often—in a previous pregnancy, were randomized to the present study at an earlier GA (24.60±6.92 ± 28.23±5.01; $P=.039$), had higher values in the OGTT, and had a higher fasting glycemia by SBGM at randomization (Table 5). Women in the

FIGURE
Trial profile



GA, gestational age.

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MET+INS group needed less quick acting INS than those in the INS-treated group: proportions of basal and rapid-acting INS were 67% and 33% for the INS-treated group and 92% and 8% for MET+INS, respectively (P=.001). There were no significant differences between women from MET-only and MET+INS groups regarding hypoglycemia.

Vitamin B12 levels (250.83±90.68 [MET] vs 240.34±67.88 pg/mL [INS]; P=.41) and triglycerides (287.66±145.07 [MET] vs 243.20±75.41 mg/dL [INS]; P=.069) were not significantly different between groups (Appendix D).

There were no observed differences in congenital anomalies in the MET- vs INS-treated groups (P=.405). The list of specific anomalies and other complications can be consulted in the Appendix E.

Diet and pharmacologic treatment were stopped at delivery. Glycemia in the postpartum OGTT did not show significant differences; the percentage of patients classified with diabetes mellitus and prediabetic states also did not show significant differences. HbA1c was lower for the MET-treated group (Table 2).

Regarding treatment acceptability (Appendix F), 70.3% of women in the MET-treated group would choose MET if pharmacologic management for GDM was needed in a subsequent pregnancy vs 32.2% of women in the INS-treated group who would choose INS again (P=.000).

Comment

Principal findings

The metformin for gestational diabetes trial has shown that MET was as effective as INS in achieving and maintaining glycemic control and successful pregnancy outcomes for women with GDM. Mean fasting and postprandial glycemia reached with MET were not different from those achieved with INS, but postprandial glycemia with MET was better for some meals. Women on INS had a higher risk of hypoglycemic episodes. Most obstetrical and perinatal

TABLE 1
Baseline characteristics

	INS-treated group (n=100)	MET-treated group (n=100)	*P* value
Age, y	34.86±4.83	34.81±5.24	.944[a]
Race or ethnic group			.323
Caucasian	86 (86)	81 (81)	
Maghrebi	9 (9)	9 (9)	
Sub-Saharan	0 (0)	3 (3)	
Hispanic	5 (5)	7 (7)	
Family history of diabetes mellitus[b]	59 (59)	58 (58)	.953
GDM in a previous pregnancy[c]	25/77 (32.5)	30/74 (40.5)	.258
Diet alone	14 (17.7)	18 (24)	.635
Insulin required	11 (13)	12 (16)	
BMI before pregnancy,[d] kg/m^2	30.42±5.42	29.89±5.73	.512[a]
<25	16 (16)	21 (21)	
25–29.9	34 (34)	32 (32)	.661
≥30	50 (50)	47 (47)	
Prepregnancy hypertension	1 (1)	4 (4)	.369
Weight, kg	85.01±16.66	84.53±15.18	.832[a]
Blood pressure, mm Hg			
Systolic	117.54±12.93	117.11±13.33	.817[a]
Diastolic	72.24±7.39	72.81±8.45	.624[e]
Nulligravid	23 (23)	26 (26)	.870
Number of previous deliveries	1.03±0.905	1.15±0.896	.405
Previous stillbirth[f]	2/77 (2.6)	4/74 (5.4)	.434
Previous macrosomia[g]	12/59 (20.3)	9/61 (15)	.694
GA at randomization, wk	26.08±6.48	27.05±5.92	.240[e]
GA at GDM diagnosis, wk	22.45±11.48	23.02±6.41	.868[e]
OGTT at 0 h, mg/dL (mmol/L)	95.32±10.27 (5.29±0.57)	92.61±10.45 (5.14±0.58)	.068[a]
OGTT at 1st h	202.52±27.75 (11.24±1.54)	201.44±29.19 (11.18±1.62)	.774[a]
OGTT at 2nd h	183.24±24.14 (10.17±1.34)	187.57±25.95 (10.41±1.44)	.248[a]
OGTT at 3rd h	147.75±34.41 (8.20±1.91)	150.09±31.35 (8.33±1.74)	.610[a]
SBGM, n/d	3.62±0.80	3.53±0.76	.410[e]
Glycemia, mg/dL (mmol/L)			
Fasting	98.56±7.75 (5.47±0.43)	96.58±9.01 (5.36±0.50)	.102[a]
Postprandial	130.45±14.41 (7.24±0.80)	127.21±11.35 (7.06±0.63)	.074[a]
After breakfast	140.9±20.72 (7.82±1.15)	138.74±18.02 (7.70±1.00)	.329[a]
After lunch	125.59±15.32 (6.97±0.85)	125.05±14.77 (6.94±0.82)	.859[a]
After dinner	127.03±17.84 (7.05±0.99)	124.5±15.86 (6.91±0.88)	.274[a]
HbA1c (%; mmol/mol)	5.3±0.36 35±3.9	5.3±0.37 35±4.0	.891[a]

BMI, body mass index; *GA*, gestational age; *GDM*, gestational diabetes mellitus; *HbA1c*, hemoglobin A1c; *INS*, insulin; *MET*, metformin; *OGTT*, oral glucose tolerance test; *SBGM*, self-blood glucose monitoring.

[a] Two-sample *t* test; [b] Diabetes mellitus in a first-degree relative; [c] Based on 151 nonnulligravid women; [d] Based on prepregnancy weight, reported in the basal visit; [e] Mann-Whitney *U* test; [f] Stillbirths; [g] Fetal weight of >4000 g, based on 120 women who had previously given birth.

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TABLE 2
Glycemic control

	INS-treated group	MET-treated group	*P* value
Glycemic control, 2 wk after randomization	n=88	n=88	
SBGM, n/d	3.76±0.99	3.51±0.69	.302[a]
Mean glycemia, mg/dL (mmol/L)			
Fasting	93.51±8.11 (5.19±0.45)	93.87±8.29 (5.21±0.46)	.736[b]
Postprandial	126.85±12.79 (7.04±0.71)	122.88±9.91 (6.82±0.55)	.080[a]
After breakfast	132.43±19.1 (7.35±1.06)	128.65±21.44 (7.14±1.19)	.231[b]
After lunch	123.78±15.68 (6.87±0.87)	116.76±14.41 (6.48±0.80)	.003[b,c]
After dinner	125.95±15.32 (6.99±0.85)	121.44±13.87 (6.74±0.77)	.041[b,c]
Hypoglycemic episodes, previous wk[d]			
Fasting/late night (n)	2	2	
After breakfast/late morning (n)	22	5	
After lunch/evening (n)	1	0	
After dinner (n)	0	0	
Mean insulin doses, IU/d	17.9±11.8		
Glycemic control, 35–37 GA	n=82	n=73	
SBGM, n/d	3.60±0.88	3.46±0.76	.567[a]
Mean glycemia, mg/dL (mmol/L)			
Fasting	88.65±8.65 (4.92±0.48)	89.19±5.95 (4.95±0.33)	.729[b]
Postprandial glycemia	123.42±13.87 (6.85±10.77)	120.36±9.01 (6.68±0.50)	.102[b]
After breakfast	127.93±21.62 (7.10±1.20)	124.68±16.22 (6.92±0.90)	.295[b]
After lunch	119.64±13.87 (6.64±0.77)	117.3±14.41 (6.51±0.80)	.287[b]
After dinner	127.39±20.54 (7.07±1.14)	118.02±12.25 (6.55±0.68)	.001[b,c]
Hypoglycemic episodes, previous wk[d]			
Fasting/late night (n)	4	1	
After breakfast/late morning (n)	24	10	
After lunch/evening (n)	4	2	
After dinner (n)	3	1	
Mean metformin doses, mg/d		1422±525 (425–2550)	
Mean insulin doses	n=78	n=15	
IU/d	35.6±30.8 (0–146)	25.3±17.7 (8–58)	.208[b]
IU/kg	0.39±0.29	0.26±0.17	.122[a]
HbA_{1c}, 35–37 GA (%, mmol/mol)	5.44±0.37 36±4.0	5.40±0.37 36±4.0	.533[b]
Women with hypoglycemia since randomization[e]	n=93	n=96	
Any hypoglycemic event (clinical or in SBGM)			
n (%)	52 (55.9)	17 (17.7)	.000[c]
OR (INS vs MET) (95% CI)	6.12 (3.13–11.94)		.000[c]
SBGM, any hypoglycemia at <70 mg/dL			
n (%)	34 (36.6)	10 (10.4)	.000[c]
OR (INS vs MET) (95% CI)	4.96 (2.77–10.80)		.000[c]

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TABLE 2
Glycemic control *(continued)*

	INS-treated group	MET-treated group	*P* value
SBGM, any hypoglycemia at <60 mg/dL			
n (%)	13 (14.1)	4 (4.2)	.025[c]
OR (INS vs MET) (95% CI)	3.78 (1.19–12.08)		.025[c]
SBGM, any hypoglycemia at <54 mg/dL			
n (%)	5 (5.4)	2 (2.1)	.209
OR (INS vs MET) (95% CI)	2.67 (0.50–14.12)		.248
Postpartum	n=80	n=71	
BMI, kg/m^2	30.86±5.7	30.04±5.78	.381[b]
Waist, cm	101.2±11.8	99.0±12.6	.296[b]
Weight change, kg (pre→postpartum)	−6.83±3.66	−6.48±3.27	.573[b]
Fasting plasma glucose, mg/dL (mmol/L)	91.71±11.89 (5.09±0.66)	89.55±11.17 (4.97±0.62)	.253[b]
2 h after OGTT glucose	110.27±39.64 (6.12±2.20)	104.50±27.21 (5.80±1.51)	.580[b]
Diabetes mellitus, n (%)	3 (3.7)	1 (1.4)	
IFG, n (%)	9 (11.2)	6 (8.4)	
IGT, n (%)	6 (7.5)	3 (4.2)	
IFG+IGT, n (%)	2 (2.5)	1 (1.4)	
Any glucose alteration	20 (25.0)	11 (15.5)	.198
HbA_{1c} postpartum (%, mmol/mol)	5.45±0.36 36±3.9	5.32±0.34 35±3.7	.023[b,c]

BMI, body mass index; *CI*, confidence interval; *HbA1c*, hemoglobin A1c; *IFG*, impaired fasting glucose[38]; *IGT*, impaired glucose tolerance; *INS*, insulin; *MET*, metformin; *OGTT*, oral glucose tolerance test; *OR*, odds ratio; *SBGM*, self-blood glucose monitoring.[38]

[a] Mann-Whitney *U* test; [b] Two-sample *t* test; [c] $P<.05$; [d] Number of episodes with glycemia at <70 mg/dL in SBGM; [e] Number of women/% of women, with at least 1 hypoglycemic episode.
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results did not show differences between groups.

Results in context

The MiG trial,[4,5] developed in Australia and New Zealand, included more than 700 women and reassured clinicians about the efficacy and safety of MET for GDM. Since then, several randomized studies examining MET compared with INS for GDM have been performed, specifically in Brazil,[10] Iran,[7,11,12] Egypt,[14,15] and Pakistan,[8,13] but, in Europe, only in Finland.[6,9]

The American Diabetes Association recommends using INS as the first pharmacologic treatment for GDM, because MET crosses the placental barrier and limited long-term offspring safety data are available.[30] Conversely, the National Institute for Health and Care Excellence guidelines propose the use of MET as a first-line treatment of GDM if blood glucose targets are not met with lifestyle changes,[24] and the Society for Maternal-Fetal Medicine considers MET a reasonable and safe first-line pharmacologic alternative to INS.[31] Protocols to offer MET as a first step in clinical practice have been implemented,[32] and its use for GDM has risen over the recent years in Northern Europe, New Zealand, and Australia, but not in the United States.[19,33] In Spain, the use of MET in pregnancy is still uncommon, because some local guidelines consider MET as alternative to INS only if the follow-up is difficult, if the woman—properly informed—refuses INS, or the risk of hypoglycemia is high.

Results and clinical implications

Mean glycemic control was not different between MET- and INS-treated groups; postprandial glycemia after lunch and dinner was significantly better for MET-treated group at the beginning of the treatment (2 weeks) and also for dinner before delivery. Other authors also reported slightly lower postprandial glucose levels for MET.[4,10,16]

We consider that the low rate of hypoglycemic events in women treated with MET, even being expected, is one of the most clinically relevant differences between groups. More than half of the women treated with INS had at least 1 hypoglycemic episode, although no one had a severe event, and most episodes were mild (60–69 mg/dL). These episodes might be in fact underrepresented, because they were not always confirmed by SBGM, because women did not check their glucose levels at every occasion and SBGM registries were obtained from only the week before every visit.

TABLE 3
Obstetrical outcomes

	INS-treated group (n=97)	MET-treated group (n=94)	*P* value
Fetal ultrasound			
Initial after enrollment			
Estimated GA	29.95±2.75	30.58±3.00	.140[a]
Estimated fetal weight, g	1621±499	1758±553	.081[a]
Abdominal circumference	30.11±2.81	30.69±3.23	.206[a]
Percentile	61.88±26.35	66.63±28.03	.243[a]
Prepartum, intended 35–37 GA			
Estimated GA	36.08±1.50	35.67±1.76	.163[b]
Estimated fetal weight	2992±385	2883±353	.061[a]
Abdominal circumference	36.43±1.66	35.80±1.91	.076[b]
Percentile	70.22±25.78	64.29±25.33	.144[a]
Weight change (prepartum to basal)	+1369±533	+1161±484	.011[a,c]
Maternal weight gain			
From prepregnancy to 36–37 GA	8.65±4.99	6.89±5.52	.046[a,c]
From prepregnancy to enrollment	4.98±5.13	6.09±5.24	.133[a]
From enrollment to 36–37 GA	3.87±3.50	1.35±3.21	.000[b,c]
Obstetrical outcomes			
Hypertensive disorders of pregnancy[d]	11 (13.56)	14 (17.5)	.247
Induction of labor	60 (62.5)	43 (45.7)	.029[c]
Elective induction of labor	29/51 (56.9)	17/39 (43.6)	.043[c]
Noninstrumental vaginal delivery[e]	38 (82.6)	58 (85.3)	.795
Cesarean deliveries	51 (52.6)	26 (27.6)	.001[c]
Elective cesarean deliveries	14 (27.4)	9 (34.6)	.144
Gestational week at birth	38.11±1.38	38.09±2.28	.192[b]
Preterm birth	12 (12.4)	12 (12.8)	.934

GA, gestational age; *INS*, insulin; *MET*, metformin.

[a] Two-sample *t* test; [b] Mann-Whitney *U* test; [c] $P<.05$; [d] Chronic hypertension+gestational hypertension+preeclampsia; [e] Noninstrumental vaginal delivery in all vaginal deliveries.

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Hypoglycemia poses not only a clinical risk but also a handicap to adjust INS doses and generates fear of the treatment. We have not found any other randomized study comparing INS with MET in GDM specifically evaluating hypoglycemia, and the reviews cite that biochemical hypoglycemia is not reported in the studies.[16] Ruholamin[12] described only 2 women having hypoglycemia on INS and none on MET, and Ashoush[15] published a nonsignificant difference for maternal hypoglycemic episodes (6 events on INS, 2 on MET plus INS, 1 on MET). These figures are so low that we think this variable was not systematically assessed.

Most obstetrical and perinatal outcomes did not show significant differences between treatment groups. Fewer cesarean deliveries were recorded in the MET-treated group, and this association remained highly significant after adjusting by several covariables. Most randomized trials have not shown this finding; only Hassan et al[8] showed an association between MET use in pregnancy and a significant reduction in the number of cesarean deliveries (33.3% on MET, 56% on INS; $P=.004$). In clinical practice, Goh et al[34] found that women treated with MET had fewer cesarean deliveries (MET, 37%; INS, 45.6%; $P=.02$). Another study in clinical practice, specifically aimed to this outcome, by Pazzagly et al[35] did not show significant differences (25.1% [MET] vs 31.7% [INS]; OR, 0.79; CI, 0.54–1.16). A recent meta-analysis[36] published a lower incidence of labor induction (relative risk [RR], 0.85; 95% CI, 0.74–0.99) and a tendency to fewer elective cesarean deliveries (RR, 0.73; 95% CI, 0.54–1.00) for MET treatment.

TABLE 4
Neonatal outcomes

	INS-treated group (n=97)	MET-treated group (n=94)	*P* value
Perinatal death	0 (0)	0 (0)	
Birth trauma	4 (4.6)	1 (1.1)	.158
Stay in NCU	9 (9.6)	7 (7.4)	.612
Respiratory distress syndrome	9 (9.6)	6 (6.4)	.592
Neonatal hypoglycemia	21 (22.3)	15 (16.3)	.298
Jaundice requiring phototherapy	8 (8.7)	7 (7.6)	.788
Any neonatal adverse event[a]	28 (30.4)	22 (23.7)	.192
Apgar score at 1 min	8.65±1.1	8.8±0.55	.875[b]
Apgar score at 5 min	9.77±0.55	9.83±0.45	.623[b]
Gender (female/male)	49/48	35/59	.064
Birthweight, g	3233.58±514.26	3171.21±599.39	.441[c]
Birthweight at the <10th percentile	6 (6.1)	8 (8.5)	.490
Birthweight at the >90th percentile	19 (19.6)	14 (14.9)	.410
Birthweight of >4000 g	4 (4.1)	4 (4.2)	.964
Birth length, cm	49.76±2.66	49.54±2.92	.364[c]
Head circumference, cm	33.45±3.05	33.76±2.15	.606[c]
All congenital anomalies	7 (7.2)	4 (4.2)	.406

INS, insulin; *MET*, metformin; *NCU*, neonatal care unit.

[a] At least 1 of the following complications: perinatal death, birth trauma, stay in NCU, respiratory distress, neonatal hypoglycemia, or jaundice requiring phototherapy; [b] Mann-Whitney *U* test; [c] Two-sample *t* test.

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We did not observe any differences in neonatal outcomes in the MET- vs INS-treated group, although others have reported an association between MET use and reduced neonatal hypoglycemia,[8,10,13,14,17] lower rates of NCU admissions,[8,11,13] and fewer macrosomic or LGA babies.[7,8,34] In addition, we did not observe any differences in hypertensive disorders of pregnancy between the 2 treatment groups, despite studies reporting the contrary.[13,16] We did find a trend of lower gestational weight gain in women in the MET- vs INS-treated group, as it has been reported elsewhere.[7,8,10,13,14,16–18]

In our study, 21.3% of the women in the MET-treated group required additional INS, in the lower range of other studies (14% to 55.8%)[7,37] and far from the figure from the MiG trial (46.3%).[4] In Europe, our figure is similar to the one published in Finland by Tertti et al[9] (20.9%), but in the United Kingdom that figure is far higher (55.8%).[37] The characteristics of women needing INS were similar to those described in the literature.[4,6,8–10,13,37]

MET is associated to well-known gastrointestinal adverse effects, commonly transient and mild, leading to therapy discontinuation in 1.9% of cases and to dose reduction in 8.8%.[4] In our patients, gastrointestinal symptoms were a common complaint, more frequently reported by women on MET, but mild and well tolerated, and leading to MET discontinuation only in 4 women (4.2%).

Other authors have also published that women treated with MET[4] or being offered the chance to use it[32] were more satisfied with the treatment.

Research implications

It would be of great interest to evaluate glycemic profiles with subcutaneous continuous monitoring devices and also to compare new long-acting formulations of INS among them and with MET.

Strengths and limitations

As far as we know, this is the first randomized trial conducted in our geographic area. Most randomized studies performed after the MiG trial[4] included fewer patients than the ours did; only Mesdaghinia et al[11] included 200 women.

This study used detemir and aspart as basal-bolus therapy. Almost all studies[7,8,10–14] describe the use of NPH and/or regular INS, in many cases premixed, or the type of INS is not described.[4] Only in Finland[6,9] Lispro or aspart were used as prandial INS, but with NPH as basal INS.

Another strength of our study is the systematic evaluation of the hypoglycemic events.

As a limitation, our results cannot be generalized to all women with

TABLE 5
Women on metformin-treated group requiring additional insulin: baseline characteristics

	MET-only group (n=70)	MET+INS group (n=20)	*P* value
Age, y	34.84±5.75	33.75±3.85	.209[a]
Family history of diabetes mellitus[b]	37 (52.9)	15 (75.0)	.088
GDM in a previous pregnancy[c]	19/53 (35.8)	9/15 (60)	.045[d]
Diet alone	14 (73.68)	3 (33.3)	
Insulin required	5 (26.31)	6 (66.6)	
BMI before pregnancy,[e] kg/m^2	29.75±6.26	30.65±4.58	.313[a]
<25	18 (25.7)	2 (10.0)	
25–29.9	22 (31.4)	6 (30.0)	.257
≥30	30 (42.9)	12 (60.0)	
Prepregnancy hypertension	3 (4.28)	1 (5.0)	.431
Blood pressure at enrollment			
Systolic	117.03±13.21	117.85±14.24	.570[a]
Diastolic	72.24±7.96	73.85±8.09	.298[f]
Nulligravid	44 (62.9)	12 (60.0)	.816
Previous stillbirth[g]	2/53 (3.78)	2/15 (13.33)	.165
Previous macrosomia[h]	6/44 (13.63)	2/13 (15.38)	.972
GA at randomization	28.23±5.01	24.60±6.92	.039[d,f]
GA at GDM diagnosis	23.48±6.15	22.19±6.82	.466[f]
OGTT at 0 h, mg/dL	91.71±10.81	97.48±9.91	.047[a,d]
OGTT at 1st h	198.92±30.81	217.3±19.64	.007[a,d]
OGTT at 2nd h	185.41±25.77	195.14±32.25	.401[a]
OGTT at 3rd h	150.81±29.37	147.21±43.96	.881[a]
Glycemic control at randomization			
SBGM, n/d	3.48±0.73	3.86±0.74	.192[f]
Glycemia, fasting, mg/dL	95.5±9.01	101.26±9.55	.002[a]
Postprandial	126.85±10.27	128.29±10.63	.797[a]
After breakfast	138.74±18.92	134.95±16.22	.450[a]
After lunch	122.88±13.69	130.81±15.5	.064[a]
After dinner	124.68±15.86	124.5±13.33	.983[a]
HbA_{1c}, %	5.3±0.37	5.3±0.39	.645[a]
HbA_{1c}, mmol/mol	34±4.0	34±4.3	

BMI, body mass index; *GA*, gestational age; *GDM*, gestational diabetes mellitus; *HbA1c*, hemoglobin A1c; *INS*, insulin; *MET*, metformin; *OGTT*, oral glucose tolerance test; *SBGM*, self-blood glucose monitoring.

[a] Two-sample *t* test; [b] Diabetes mellitus in a first-degree relative; [c] For nonnulligravid women; [d] $P<.05$; [e] Based on prepregnancy weight reported in the basal visit; [f] Mann-Whitney *U* test; [g] After the 20th week of pregnancy; [h] Infant weight of >4000 g.

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GDM who need pharmacologic treatment, because those with overt fasting hyperglycemia (>120 mg/dL) were excluded. Another limitation is that, because this was an open-label study, the obstetricians assisting with the deliveries (most of them not involved in the study) might have considered that the use of INS could be associated with a worse GDM profile; this could have posed a significant source of bias for the outcomes of induction of labor and/or cesarean deliveries.

Conclusions

For women with GDM needing pharmacologic treatment, MET can achieve

the same glycemic control as INS, with fewer hypoglycemic events, and mostly the same obstetrical and perinatal results. Women should be informed about the off-label use of MET in pregnancy and the uncertainties about the future anthropometry of the children, but reassured about the efficacy and safety of MET regarding pregnancy itself. ■

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Appendix A

Insulin regimen

Detemir insulin, if needed, was always administered before bed. NovoRapid insulin, if needed, was always administered before the main meals. Not all the patients needed 4 doses of insulin a day in a basal-bolus complete regimen. Depending on the glycemic profile, women were treated with any of the following regimens: basal insulin alone, if fasting glycemia was above targets; quick acting insulin (1−3 times a day), if postprandial glycemic levels were above targets; and a combination of basal and quick acting insulins, if both fasting and postprandial levels were above targets. It was common that women starting their insulin treatment only with basal insulin, or only insulin for breakfast, as pregnancy progressed needed a more complex regimen.

Insulin adjustments

We asked the women not to wait for a whole week to adjust insulin. If 2 glucose values were elevated in the same week (eg, Tuesday and Wednesday) without an evident explanation (eating during the night, a fever, a bad night, etc), they had to increase insulin by 2 UI from then on. If again in the same week 2 values were elevated, insulin had to be increased again. Then they could increase insulin up to 3 times a week (6 UI) if glucose figures were clearly and consistently above targets.

The same number and frequency of elevated postprandial glucose values were used to adjust quick insulin doses, provided that hypoglycemic episodes did not happen at 2 to 4 hours of insulin administration. It is not uncommon for pregnant women to show a high glucose figure 1 hour after breakfast, but low to normal 2 hours after that meal, and even a low figure since that time on. In that case, the composition of breakfast had to be further modified or even a second breakfast (dairy product or fruit) was introduced to avoid hypoglycemia in the morning, before new increases of insulin doses were made.

Treatment compliance

Metformin (coming from the hospital pharmacy) was delivered in every endocrinology visit; we have records of the dispensing of every metformin pack in the women's histories, but we did not ask them to bring back every empty container. In addition, through the outpatient's electronic prescription, individual insulin collection from the drugstore could be consulted. However, this aspect has not been systematically evaluated for all the patients yet. It was checked by the endocrinologist—at 1 or more visits—for some specific patients, when there were doubts about their compliance. Some women completely abandoned insulin treatment on their own, at least for a period of time, and obviously they were not offered metformin; they were withdrawn from the study and were strongly advised to be adherent to their medication regardless of the clinical trial. Because the data were analyzed on an intention-to-treat basis, they were included in some of the subanalyses.

Appendix B
Additional information on inductions of labor, cesarean deliveries, and preterm births

SUPPLEMENTAL TABLE 1
Reasons reported for labor inductions

Labor inductions	INS	MET	*P* value
1. Elective inductions:	29	17	.043
2. Other inductions:			
Fetal reasons	4	3	
Macrosomia	1	0	
Meconium	2	1	
Fetal aorta coarctation	0	1	
FGR	1	1	
Obstetrical reasons	6	10	
Overdue pregnancy	0	1	
Metrorrhagia	0	1	
Premature rupture of membranes	4	8	
Oligoamnios	2	0	
Maternal reasons	12	9	
Hypertension (all)	11	9	
Cholestasis gravidarum	1	0	
Total	51	39	.08

Total number of cases with induction of labor: INS-treated group, 60 (62.5%); MET-treated group, 43 (45.7%); *P*=.029.

FGR, fetal growth rate; *INS*, insulin; *MET*, metformin.

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SUPPLEMENTAL TABLE 2
Reasons reported for elective cesarean deliveries

Elective cesarean deliveries	INS	MET	*P* value
On request	2	0	
Iterative	2	7	
Myomectomy	2	0	
Breech presentation	4	2	
Macrosomia	1	0	
Birth canal dystocia	1	0	
Placenta previa	1	0	
Severe FGR	1	0	
	14	9	

FGR, fetal growth rate; *INS*, insulin; *MET*, metformin.

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SUPPLEMENTAL TABLE 3
Reasons reported for preterm births

Preterm births	INS	MET
Spontaneous preterm labor	1	1
PPROM	6	7
Therapeutic preterm birth	2	1
Severe IUGR	1	-
Severe Preeclampsia	-	1
Placenta previa	1	-
	9	9

Total number of cases with preterm birth: INS-treated group, 12 (12.4%); MET-treated group, 12 (12.8%); *P*=.934. Information is lacking in 2 cases who gave birth in private clinics. In the other 2 cases, the GA at delivery was recorded as 36+6 vs 37+1 depending on the report; we have omitted them.

INS, insulin; *IUGR*, intrauterine growth restriction; *MET*, metformin; *PPROM*, preterm premature rupture of membranes.

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Appendix C

SUPPLEMENTAL TABLE 4
Obstetrical and neonatal outcomes after exclusion of patients who had to discontinue metformin because of intolerance

	INS-treated group (n=97)	MET-treated group (n=90)	*P* value
Maternal weight gain			
From prepregnancy to 36–37 GA	8.65±4.99	6.88±5.55	.043[a,b]
From prepregnancy to enrollment	4.98±5.13	5.97±5.27	.185[b]
From enrollment to 36–37 GA	3.87±3.50	1.35±3.28	.000[a,c]
Obstetrical outcomes			
Hypertensive disorders of pregnancy[d]	11 (13.5)	13 (14.4)	.210
Induction of labor	60 (62.5)	41 (45.6)	.020[a]
Noninstrumental vaginal delivery[e]	38 (82.6)	56 (84.8)	.949
Cesarean delivery	51 (52.6)	24 (26.6)	.001[a]
Gestational week at birth	38.11±1.38	38.07±2.35	.426[c]
Preterm birth	12 (12.4)	11 (12.2)	.975
Perinatal outcomes			
Birth trauma	4 (4.6)	1 (1.1)	.186
Stay in NCU	9 (9.6)	7 (7.8)	.649
Respiratory distress syndrome	9 (9.6)	6 (6.7)	.472
Neonatal hypoglycemia	21 (22.3)	15 (16.7)	.448
Jaundice with phototherapy	8 (8.7)	7 (7.8)	.857
Any neonatal adverse event[f]	28 (30.4)	22 (24.4)	.390
Apgar score at 1 min	8.65±1.1	8.9±0.56	.969[c]
Apgar score at 5 min	9.77±0.55	9.82±0.46	.713[c]
Birthweight, g	3233.58±514.26	3181.76±606.29	.528[b]

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SUPPLEMENTAL TABLE 4

Obstetrical and neonatal outcomes after exclusion of patients who had to discontinue metformin because of intolerance *(continued)*

	INS-treated group (n=97)	MET-treated group (n=90)	*P* value
Birthweight at the <10th percentile	6 (6.1)	8 (8.9)	.433
Birthweight at the >90th percentile	19 (19.6)	14 (15.5)	.427
Birth length, cm	49.76±2.66	49.64±2.82	.755[b]

GA, gestational age; *INS*, insulin; *MET*, metformin; *NCU*, neonatal care unit.

[a] $P<.05$; [b] Two-sample *t* test; [c] Mann-Whitney *U* test; [d] Chronic hypertension+gestational hypertension+preeclampsia; [e] Noninstrumental vaginal delivery in all vaginal deliveries; [f] At least 1 of the following complications: perinatal death, birth trauma, stay in NCU, respiratory distress, neonatal hypoglycemia, or jaundice requiring phototherapy.

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Appendix D

Vitamin B12 and triglyceride levels

Because metformin may lead to vitamin B12 deficiency,[1] causing questions regarding its safe use in pregnancy, we examined vitamin B12 levels in all participants and found no difference between the MET- or INS-treated groups (250.83 pg/mL±90.68 [MET] vs 240.34±67.88 [INS]; $P=.41$).

Similarly, we examined potential effects of insulin and metformin on triglyceride levels, which are significantly elevated in women with GDM[2] and associated with fetal overgrowth.[3,4] Studies have shown that insulin may reduce triglyceride levels[5]; however, we found no difference in triglycerides in the MET- and INS-treated groups (287.66 mg/dL ±145.07 vs 243.20±75.41; $P=.069$).

Supplemental References

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Appendix E

Congenital anomalies and other complications detected in the babies

Major congenital anomalies: 1 aorta coarctation requiring surgery (MET-treated group)

Minor congenital anomalies: 7 infants in INS- and 3 in MET-treated groups had minor malformations

INS: 1 choanal stenosis, 1 lumbar myelocystocele+4th to 5th toe agenesis, 1 clinodactyly in 1 foot+bilateral hallux valgus, 1 club feet, 1 coloboma, 2 cryptorchidisms

MET: 1 hypospadias, 1 left superior vena cava, 1 pyelocaliceal dilation (P=.405)

Other complications: 1 single case had shoulder dystocia, 1 case of pulmonary hypertension case requiring medical treatment (MET), another baby had neonatal cerebral and ventricular bleeding requiring ventriculoperitoneal shunt (INS), 1 infant (INS) was admitted to NCU because of lactic acidosis, bearing a severe defect in the mitochondrial respiratory chain complex I and dying at 3 months of life.

Appendix F

SUPPLEMENTAL TABLE 5
Questionnaire on acceptability of the treatment

	INS-treated group	MET-treated group	*P* value
How often did you forget to take your medication?	n= 87	n=82	
Never or rarely	77 (88.5)	76 (92.7)	.412
1–3 times/wk	9 (10.3)	5 (6.1)	
4–6 times wk	0 (0)	1 (1.2)	
>6 times wk	1 (1.1)	0	
Which medication would you choose in another pregnancy?	n= 87	n=82	
Metformin tablets	36 (41.4)	58 (70.3)	**.000**[a]
Insulin injections	28 (32.2)	8 (9.7)	
Not sure	23 (26.4)	16 (19.5)	
In another pregnancy, if you were told you were likely to need insulin injections to control the sugar levels, but you could try metformin first, what would you prefer?	n= 87	n=82	
Start with metformin, add insulin if needed	55 (63.2)	73 (89.0)	**.001**[a]
Go straight to insulin injections	19 (21.8)	4 (4.9)	
Not sure	13 (14.9)	5 (6.1)	
Which part of your diabetes mellitus treatment was the easiest?	n=86	n= 80	
Doing finger-prick tests	44 (51.2)	28 (35.0)	.171
Being careful with the diet	17 (19.8)	22 (27.5)	
Taking medication	25 (29.1)	30 (37.5)	
Which part of your diabetes mellitus treatment was the hardest?	n=86	n=80	
Doing finger-prick tests	28 (32.6)	24 (30.0)	.355
Being careful with diet	37 (43.0)	43 (53.7)	
Taking medication	21 (24.4)	13 (16.2)	

INS, insulin; *MET*, metformin.

[a] $P<.05$.

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