OBSTETRICS

Randomized trial of metformin vs insulin in the management of gestational diabetes

Cristiane Pavão Spaulonci, MD; Lisandra Stein Bernardes, PhD; Thatianne Coutheux Trindade, MD; Marcelo Zugaib, MD, PhD; Rossana Pulcineli Vieira Francisco, MD, PhD

OBJECTIVE: To evaluate glycemic control in women receiving metformin or insulin for gestational diabetes, and to identify factors predicting the need for supplemental insulin in women initially treated with metformin.

STUDY DESIGN: Women with gestational diabetes who failed to achieve glycemic control with diet and exercise were randomized to receive metformin (n = 47) or insulin (n = 47). Criteria for inclusion were singleton pregnancy, diet, and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus. Patients who were lost to prenatal follow-up were excluded.

RESULTS: Comparison of mean pretreatment glucose levels showed no significant difference between groups ($P = .790$). After introduction of the drug, lower mean glucose levels were observed in the metformin group ($P = .020$), mainly because of lower levels after dinner ($P = .042$). Women using metformin presented less weight gain ($P = .002$) and a lower frequency of neonatal hypoglycemia ($P = .032$). Twelve women in the metformin group (26.08%) required supplemental insulin for glycemic control. Early gestational age at diagnosis (odds ratio, 0.71; 95% confidence interval, 0.52—0.97; $P = .032$) and mean pretreatment glucose level (odds ratio, 1.061; 95% confidence interval, 1.001—1.124; $P = .046$) were identified as predictors of the need for insulin.

CONCLUSION: Metformin was found to provide adequate glycemic control with lower mean glucose levels throughout the day, less weight gain and a lower frequency of neonatal hypoglycemia. Logistic regression analysis showed that gestational age at diagnosis and mean pretreatment glucose level were predictors of the need for supplemental insulin therapy in women initially treated with metformin.

Key words: gestational diabetes, insulin, metformin, randomized trial

Cite this article as: Spaulonci CP, Bernardes LS, Trindade TC, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol 2013;209:34.e1-7.

Gestational diabetes (GDM) is observed in 7% to 18% of pregnancies.[1] Possible complications include a higher frequency of fetal macrosomia, preeclampsia, cesarean section, and neonatal hypoglycemia, all of which are substantially reduced when glucose levels are controlled, either by diet and exercise primarily or through medication when the first approach proves insufficient.[2] Standard treatment for achieving adequate glucose levels is insulin therapy.[3] However, this therapy requires multiple daily injections of insulin, which may reduce patient adherence. Furthermore, its high cost may preclude treatment for some patients.

Oral antidiabetic agents have been investigated as an alternative to insulin therapy because of their ease of use and lower cost.[4] Metformin is a biguanide hypoglycemic agent that reduces hepatic gluconeogenesis and increases peripheral insulin sensitivity. Over the past few years, a number of studies have investigated the use of metformin for the treatment of GDM and 2 randomized trials have shown similar neonatal results, concluding that metformin seems to be an effective alternative for the treatment of GDM.[4-10] However, response to treatment in patients with gestational diabetes is highly dependent on patient characteristics.[11]

Considering that neonatal outcomes hinge on the adequacy of metabolic control, the primary objective of the present study was to compare glycemic control in women who received metformin or insulin for the treatment of GDM in our population. Because some patients receiving metformin do not achieve adequate glucose control, consequently having to receive insulin, a second objective was to identify factors that could predict the need for supplemental insulin in women initially treated with metformin.

Materials and Methods

Ninety-two women diagnosed with GDM, who received prenatal care at the Obstetrics Clinic of Hospital das Clinicas, Sao Paulo University School of Medicine (HC-FMUSP), Sao Paulo, Brazil, were studied prospectively between Nov. 1, 2007, and Jan 31, 2010.

From the Department of Obstetrics and Gynecology, Hospital das Clínicas, University of São Paulo, Brazil.

Received Nov. 30, 2012; revised Feb. 6, 2013; accepted March 16, 2013.

Clinical trial registration: Umin Clinical Trials Registry, http://www.umin.ac.jp/ctr/index.htm. UMIN 000005393.

The authors report no conflict of interest.

Reprints: Rossana Pulcineli Vieira Francisco, MD, PhD, Av. Dr. Enéas de Carvalho Aguiar, n.255, sala 10085, São Paulo, SP, Brazil, 05403-000. rpvf@uol.com.br.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2013.03.022

Criteria for inclusion were singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis (renal failure, heart failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic phenomena), and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography. Patients were included after they had signed the free informed consent form. The study was approved by the Ethics Committee of the Clinical Board of the HC-FMUSP (no. 0530/2007). Patients lost to prenatal follow-up were excluded.

A diagnosis of GDM at the time of the study was established when the patient presented 2 or more altered results on the oral glucose tolerance test with 100 or 75 g glucose, according to the criteria of the American Diabetes Association (ADA).[12] Values of glucose considered normal were as follows: 95 mg/dL at 0 minutes, 180 mg/dL at 60 minutes, 155 mg/dL at 120 minutes, and 140 mg/dL at 180 minutes. After the diagnosis of GDM, the women were referred for follow-up to an outpatient clinic specialized in diabetes and pregnancy. On the first prenatal visit, information on demographic was obtained and clinical data collected. For nutritional counseling, a calorie intake of 25 to 35 kcal/kg weight per day was recommended depending on the classification of the pregestational body mass index (BMI) of the patient. In addition, the calories were divided to comprise 55% carbohydrates, 15% proteins, and 30% lipids. A 30-minute walk, 3 times a week, was recommended as exercise. For glucose monitoring, a fingertip capillary blood sample was obtained 4 times per day (at fasting, 2 hours after breakfast, 2 hours after lunch, and 2 hours after dinner). The patients were asked to record all capillary glucose measurements and the memory of the glucose meters was tested weekly. The glucose reference values recommended by the ADA were used: fasting ($\leq$95 mg/dL) and 2 hours after a meal ($\leq$120 mg/dL).[13] Patients were excluded if they had performed less than 85%b of the tests.

Unsatisfactory glycemic control was defined among patients who presented more than 30% of capillary glycemia results above the reference values 1 week after commencing diet therapy combined with physical activity. Medication-based treatment was then initiated. At this time, patients who met all inclusion criteria were randomized to receive either metformin (study group) or insulin (control group) according to an electronic randomization list. Data were collected weekly during return visits.

The control group received human NPH insulin. The starting dose was 0.4 units per kg body weight per day, with half the dose being administered in the morning (before breakfast), $^1/_4$ of the total dose before lunch, and $^1/_4$ at 22:00 hours. This group was asked to monitor glucose 7 times per day (at fasting, 2 hours after breakfast, 1hour before lunch, 2 hours after lunch, 1 hour before dinner, 2 hours after dinner and at 3 in the morning). The doses were adjusted weekly to achieve adequate glycemic control. If preprandial glucose levels were normal and postprandial glucose levels were high, regular insulin was added half an hour before that meal in addition to NPH insulin.

The metformin group received an initial metformin dose of 1700 mg/d (850 mg 3 times a day) and if adequate control was not achieved the dose was raised the next week to 2550 mg/d (850 mg twice a day). Patients who did not achieve satisfactory glycemic control with metformin received supplemental insulin. The data were analyzed on an intention to treat basis. Adequate control was defined for both groups as having less than 30% of capillary glycemia results above the reference values during 1 week of treatment.

Compliance was defined as having performed at least 85% of the scheduled capilar glicemias.

The women were followed up until delivery and the occurrence of preeclampsia, prematurity (birth before 37 weeks of gestation), and neonatal outcomes. Preeclampia was defined by the appearance of hypertension after 20 weeks of gestation associated to edema and proteinuria. Superimposed preeclampsia was defined as worsening of tension levels associated to edema and appearance or worsening of proteinuria in women with chronic hypertension predating pregnancy. Neontal outcomes were hypoglycemia (capillar glicemia inferior to 40 mg/dL in the first 48 hours of life), macrosomia (neonatal weight equal or superior to 4000 g), hyperbilirubinemia, and SIRS.

All neonates had capilar glicemia tested at 1.5 hours of life, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours of life, and if they had symptoms.

Patients using metformin were actively asked about side effects symptoms: nausea, vomiting, and frequency of bowel movements.

The sample size was calculated assuming a difference in mean glucose level of 15 mg/dL between groups, a standard deviation of 20 mg/dL, level of significance of 5%, and power of the test of 90%. The estimated number of patients, assuming a 10% loss of subjects in each group, was 82, comprising 41 patients per group.[14,15]

Mean glucose levels obtained during the whole follow-up period, from introduction of medication to birth, were compared at each time of the day by analysis of variance with repeated measures for the comparison of treatments. When a significant difference was detected, Tukey's multiple comparison test was applied to verify if there was a difference between groups at any specific period.

Numerical variables were compared by the Student t test or Mann-Whitney test. The χ^2 test, Fisher exact test or likelihood ratio tests were used to compare categorical variables. In addition, logistic regression analysis was performed to predict the need for supplemental insulin in women initially treated with metformin. Individual variables that showed a significant difference between metformin and 'metformin + insulin' groups were selected for entry to the multiple logistic regression model. A level of significance of 5% was adopted for all tests.

RESULTS

The initial sample consisted of 94 women who were randomized into the

metformin group (group 1, n = 47) or the insulin group (group 2, n = 47). Two women were excluded for discontinuing prenatal care (1 from each group). This gave a final sample of 92 women (46 in the metformin group and 46 in the insulin group) (Figure 1).[16] One of the women who presented metformin intolerance wished to discontinue the medication and human NPH was therefore introduced. For the purposes of data analysis, this patient belonged to group 1. No patients were excluded because of lack of compliance.

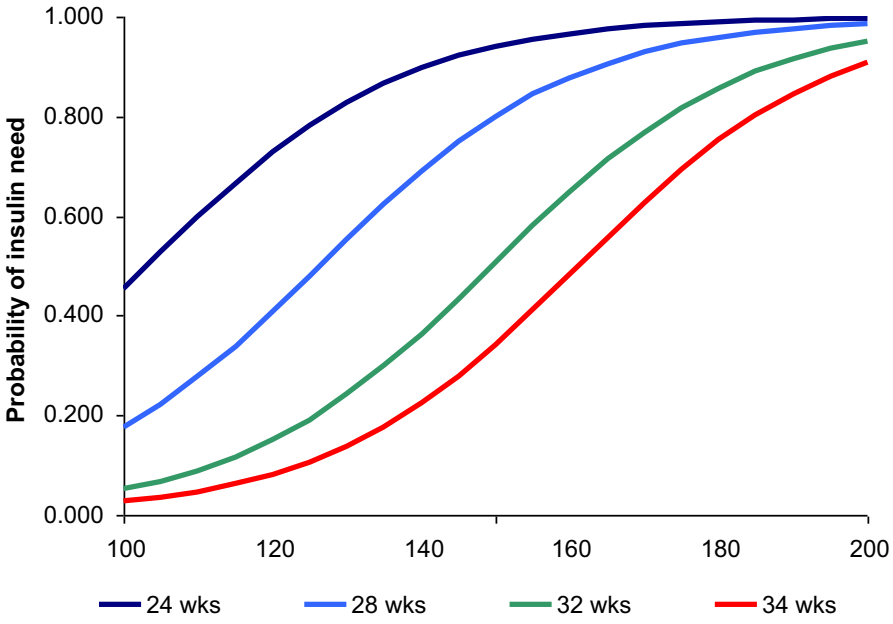
Demographic and baseline clinical data

No significant differences between groups were observed in terms of maternal age, parity, gestational age at diagnosis of GDM, gestational age at the beginning of medication-based treatment, pregestational BMI, BMI at diagnosis, BMI at the beginning of medication-based treatment, or glycated hemoglobin (HbA1C) at diagnosis (Table 1). However, there was a significant difference in the number of pregnancies between groups, with a median number of 2 pregnancies in group 1 vs 3 pregnancies in group 2 ($P = .035$). No significant difference between groups was observed regarding the proportion of nulliparous women (10/46 [21.7%] in group 1 and 17/46 [37%] in group 2; $P = .109$), frequency of chronic hypertension predating pregnancy (14/46 [30.4%] in group 1 and 12/46 [26.1%] in group 2; $P = .643$), or frequency of smoking (2/46 [4.3%] in group 1 and 5/46 [10.9%] in group 2; $P = .434$). There was also no difference in the number of patients having previous cesarean-sections. In the group insulin 20 patients (43%) had at least 1 previous cesarean-section and in the group metformin 17 patients (36.9%) had at least 1 previous c-section ($P = .524$).

Weight gain

With respect to weight gain, less gain was observed in the metformin group between the diagnosis of GDM and delivery (group 1: 0.53 ± 2.52 kg vs group 2: 2.3 ± 2.77 kg; $P = .002$) and between the beginning of medication-based treatment and delivery (group 1: 0.43 ± 1.99 kg vs group 2: 2.07 ± 2.39 kg; $P = .001$).

FIGURE 1
Probability of need for supplemental insulin



Estimated probability of need for supplemental insulin in women with gestational diabetes receiving metformin according to mean pretreatment glycemia and gestational age at diagnosis of gestational diabetes.

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

Pregnancy outcome

The 2 groups did not differ in terms of the frequency of preeclampsia (10/46 [21.7%] in group 1 and 7/46 [15.2%] in

TABLE 1
Characteristics of the pregnant women studied

Variable	Metformin group	Insulin group	*P* value
Age, y	31.93 ± 6.02	32.76 ± 4.66	.464
Number of pregnancies	2 (1-8)	3 (1-8)	.035[a]
Parity	1 (0-5)	1 (0-6)	.072
GA at the time of diagnosis of gestational diabetes	30.40 ± 3.71	30.63 ± 3.35	.756
GA at the beginning of treatment	32.18 ± 3.70	32.05 ± 3.50	.864
Pregestational BMI	28.68 ± 5.60	27.99 ± 5.86	.563
BMI at diagnosis	31.97 ± 4.71	31.31 ± 5.80	.549
BMI at the beginning of treatment	31.96 ± 4.75	31.39 ± 5.71	.603
HbA1C at diagnosis	5.90 ± 0.75	5.93 ± 0.80	.863

Results are reported as the mean ± standard deviation for parametric variables and median (min-max) for nonparametric variables.

BMI, body mass index (kg/m^2); *GA*, gestational age (wks); *HbA1C*, glycated hemoglobin (%).

[a] Statistically significant.

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

TABLE 2
Neonatal outcomes in the metformin and insulin group for continuous variables

Variable	Metformin group	Insulin group	*P* value
Gestational age at birth	38.33 ± 1.45	38.24 ± 1.53	.776
1-min Apgar score	9 (4-10)	9 (0-10)	.980
5-min Apgar score	10 (0-10)	10 (0-10)	.188
Umbilical artery pH at birth	7.22 ± 0.07	7.22 ± 0.08	.824
Newborn weight	3143.7 ± 446.6	3237.6 ± 586.8	.390

Results are reported as the mean ± standard deviation for parametric variables and median (min-max) for nonparametric variables.

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

group 2; $P = .420$), Of those, preeclampsia was superimposed to chronic hypertension in 5 patients that had chronic hypertension in group 1 (5/14, 35.7%) and in 3 patients (3/12, 25%) in group 2 ($P = .683$). The 2 groups did not differ in terms of prematurity (5/46 [10.9%] in group 1 and 5/46 [10.9%] in group 2; $P > .99$), and cesarian section (33/46 [71.7%] in group 1 and 30/46 [65.2%] in group 2; $P = .774$).

Neonatal outcomes

No significant differences between the 2 groups were observed regarding the following neonatal outcomes: gestational age at birth (group 1: 38.33 ± 1.45 weeks vs group 2: 38.24 ± 1.53 weeks; $P = .776$), 1-minute Apgar score (group 1: 9 [0-10] vs group 2: 9 [4-10]; $P = .980$), 5-minute Apgar score (group 1: 10 [0-10] vs group 2: 10 [0-10]; $P = .188$), umbilical artery pH at birth (group 1: 7.22 ± 0.07 vs group 2: 7.22 ± 0.08; $P = .824$), or newborn weight (group 1: 3143.7 ± 446.6 g vs group 2: 3237.6 ± 586.8 g; $P = .390$) (Table 2). There were no fetuses with macrosomia in the group metformin vs 3 (6.5%) cases in the insulin group ($P = .242$). In the group receiving metformin 6 neonates (13%) were small for gestational age (SGA), 38 (82.6%) were adequate for gestational age (AGA) and 2 (4.3%) were large for gestational age (LGA). In the group receiving insulin 4 neonates (8.7%) were SGA, 39 (84.8%) were AGA, and 3 (6.5%) were LGA ($P = .735$).

A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (10/46, 22.2%) compared with newborns from the metformin group (3/46, 6.5%) ($P = .032$) (Table 3).

Metformin side effects

Twenty-one (45.65%) of the 46 women who received metformin reported some side effect. The most frequent symptom was nausea, reported by 8 (38%) women. Seven (33%) patients reported an increased frequency of bowel movements and 3 (14.28%) reported the triad of nausea, vomiting, and increased frequency of bowel movements. Only one woman had epigastralgia and constipation and preferred to stop metformin and to start taking insulin.

TABLE 3
Neonatal outcomes in the metformin and insulin group for categorical variables

	Metformin group		Insulin group		
Variable	n	%	n	%	*P* value
Macrossomia	0	0	3	6.5	.242
Neonatal hypoglicemia	6.5	13	10	22.2	.032[a]
Respiratory distress syndrome	7	15.2	7	15.2	.964
Hyperbilirrubinemia	4	8.7	5	11.1	.739

[a] Statistically significant.

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

Glycemic control

With respect to glycemic control, no significant difference in mean pretreatment glucose levels was observed between groups ($P = .790$). However, after introduction of the drugs, higher mean glucose levels were observed in the insulin group ($P = .020$), mainly because of higher levels observed after dinner ($P = .042$) (Table 4).

Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment ($P = .11$).

Glycemic control in the group of patients requiring supplemental insulin.

Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Women using metformin plus insulin were diagnosed with GDM at a younger gestational age (27.55 ± 5.25 weeks) than those using metformin alone (31.4 ± 2.36 weeks) ($P = .030$). BMI at the beginning of pregnancy, BMI and A1C at the time of study inclusion, and fasting glycemia were similar in both groups (Table 5). Mean glucose levels in the week before the beginning of medication-based treatment were higher in the metformin + insulin group than in the metformin group ($P < .001$).

Prediction of need for supplemental insulin

Logistic regression analysis showed that gestational age at diagnosis (odds ratio. 0.71; 95% confidence interval, 0.52−0.97; $P = .032$) and mean pretreatment glucose level were predictors of the need for supplemental insulin therapy in women with GDM initially treated with metformin. Thus, a probability curve of the need for a combination of metformin and

TABLE 4
Mean capillary blood glucose levels in the different periods of the day

Variable	Fasting	After breakfast	After lunch	After dinner	*P* value
Pretreatment glucose levels					.790
Metformin group	102.15 ± 21.96	120.67 ± 24.03	120.61 ± 22.63	131.22 ± 25.43	
Insulin group	100.87 ± 15.05	119.81 ± 21.59	123.72 ± 19.4	132.63 ± 23.82	
Posttreatment glucose levels					.020[a]
Metformin group	90.09 ± 16.29	107.7 ± 16.69	106.87 ± 11.16	110.76 ± 11.57[b]	
Insulin group	88.35 ± 7.45	106.45 ± 11.75	111.43 ± 8.84	119.09 ± 16.47[b]	
Pretreatment glucose levels in the groups metformin alone and metformin + insulin					< .001[a]
Metformin alone group	98.05 ± 19.03	115.41 ± 15.09	116.37 ± 15.9	125.16 ± 15.67	
Metformin + insulin group	113.98 ± 26.2	135.6 ± 36.77	132.65 ± 33.51	148.39 ± 38.41	

Results are reported as the mean ± standard deviation. Glucose levels are expressed in mg/dL.

[a] Statistically significant (analysis of variance with repeated measures); [b] Statistically significant (Tukey multiple comparison test).

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

insulin was constructed as shown in Figure 2.

Comment

The primary objective of this study was to evaluate glycemic control in women with GDM treated with metformin or insulin. After introduction of the drugs, lower mean glucose levels were observed in the group receiving metformin ($P = .020$), especially after dinner ($P = .042$). These findings demonstrate that metformin is an effective agent for achieving glycemic control in women with GDM. In addition, weight gain between diagnosis of GDM and delivery ($P = .002$) and between beginning of treatment with drugs and delivery ($P = .001$) was significantly lower in the metformin group. Similar results have been reported by Rowan et al who found less mean weight gain in the metformin group (0.4 ± 2.9 kg) than in the group treated with insulin (2.0 ± 3.3 kg).[6]

Similarly to Rowan et al[5] and Terti et al,[17] we found no significant differences in the frequency of preeclampsia, incidence of prematurity or gestational age at the time of delivery between the 2 groups. However, preeclampsia occurred in 22% of metformin treated subjects and 15% of insulin treated subjects. Although nonsignificant, this increase may be significant in a bigger sample size, and must be evaluated in further studies.

Similarly, there was no difference in the rate of cesarean-sections. However, our rate of cesarean-sections was high, in part because of a high percentage of patients that had already had a previous cesarean-section (40.2% of patients).

There was also no difference in neonatal outcomes (1- and 5-minute Apgar score, umbilical cord pH, newborn birthweight), except for the frequency of neonatal hypoglycemia, which was higher in the group receiving insulin than in the group treated with metformin.

Glycemic and neonatal outcomes were better in the metformin group, with less neonatal hypoglycemia. However, 12 women (26.08%) required supplemental insulin to achieve adequate glycemic control. This percentage is similar to that reported by Coetzee and Jackson (28.6%), but differs to rates reported by Rowan et al (46.3%), Terti et al (18%), and Moore et al (34.7%).[5,14,17] These disparities are probably explained by differences in the populations studied

TABLE 5
Characteristics of patients in the groups of women that received metformin alone and metformin + insulin

Variable	Metformin	Metformin + insulin	*P* value
GA at the time of diagnosis of gestational diabetes	31.4 ± 2.36	27.55 ± 5.25	.03[a]
Pregestational BMI	29.01 ± 5.73	27.73 ± 5.35	.502
BMI at diagnosis	32.04 ± 4.7	31.77 ± 4.92	.87
HbA1C at diagnosis	5.82 ± 0.53	6.11 ± 1.17	.428
Fasting glicemia	98.05 ± 19.03	113.98 ± 26.2	.249

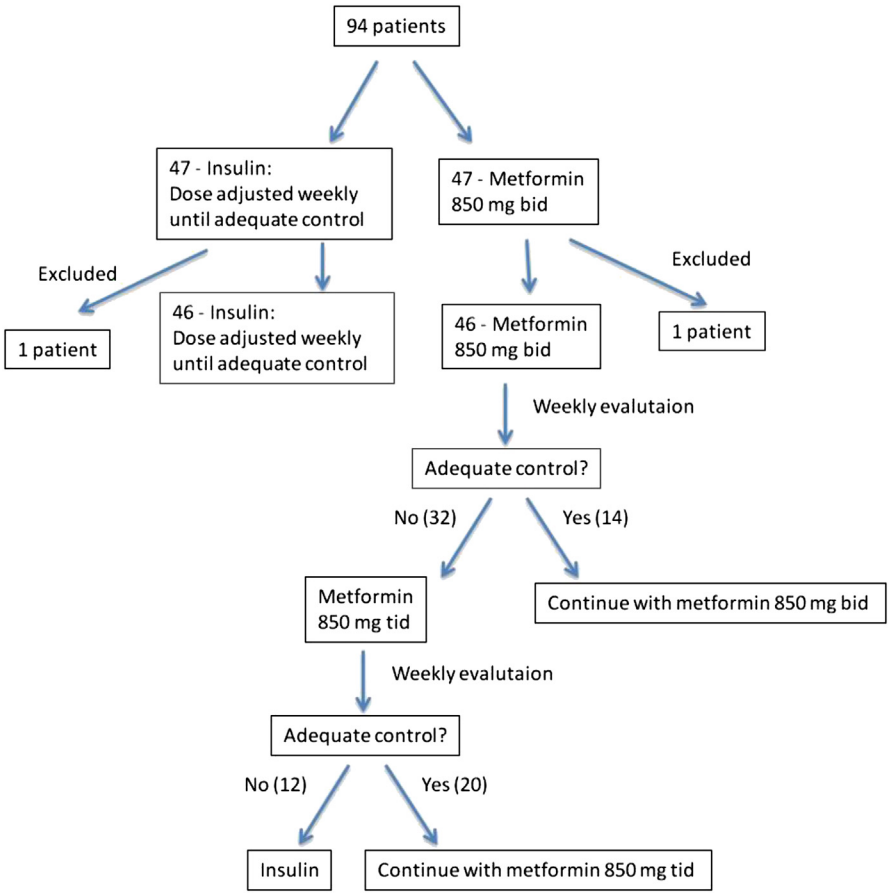
Results are reported as the mean ± standard deviation. Fasting glicemia (mg/dL).

GA, gestational age (wks); *BMI*, body mass index (kg/m^2); *HbA1C*, glycated hemoglobin (%).

[a] Statistically significant.

Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

FIGURE 2
Consort flow diagram of patients included in the study



Spaulonci. Gestational diabetes and metformin. Am J Obstet Gynecol 2013.

because diabetes and glycemic control varies widely in different populations. In fact, one of the population characteristics that might have influenced the differences in the failure rate of metformin is the body mass index of the patients evaluated. In the study of Rowan et al,[5] the BMI was greater than the observed in our study (36.7 ± 9.3 in their study and 31.77 ± 4.92 in ours).

If prediction of those patients more likely to need supplemental insulin was possible, perhaps it would be reasonable to start both medications immediately and achieve glycemic control more efficiently and in less time, achieving better neonatal results.

Logistic regression analysis in our study revealed that gestational age at diagnosis of GDM and mean glucose level (the week before introduction of medication) were predictors of the need for supplemental insulin. On the basis of these parameters, a probability curve of insulin could be constructed. We are well aware that the number of patients in the metformin+insulin group is small and that these results need to be confirmed by further studies, but this data yields clues toward predicting the need for supplemental insulin in the group started on metformin.

In the study performed by Rowan et al,[5] BMI at the beginning of pregnancy, BMI and HbA1C at the time of study inclusion, and elevated fasting glycemia predicted the need for supplemental insulin.[6] By contrast, in the current study these parameters were similar in the 2 groups, with neither BMI nor glycated hemoglobin influencing insulin need.

The use of metformin for the treatment of GDM is safe in the short-term and seems to be safe in the long-term. In a recent study, Tartarin et al[18] observed a decrease in testosterone secretion in organotypic test cultures of human and mouse cells. However, the number of germ cells was not affected in an in vivo rat model and Leydig cells were diminished only in the fetal period. Furthermore, Gilbert et al, in a metanalysis, showed no increase in risk for fetal malformations with the use of metformin in the first trimester, and the drug is FDA category B. Because neonatal results are better for metformin and the medication is less expensive than insulin, we believe that metformin should be evaluated as a possible medication for a given group of patients, especially those with a probability of receiving insulin lower than 50%. However, metformin crosses the placenta[19] and while no adverse consequences have been reported to date, long-term studies have not been carried out and there remains the possibility of in utero programming leading to changes in adulthood, which could be good or bad. Rowan et al[5] evaluated growth in 154 children whose mothers received metformin in pregnancy to 164 children whose mothers received insulin in pregnancy and observed that, although total fat mass was similar in both groups, children exposed to metformin had larger measures of subcutaneous fat.[20] So, patients should be informed of possible unknown effects of in utero exposure to metformin.

A high frequency of patients receiving metformin (45.65%) reported side effects at some time during prenatal care. However, our study was not designed to evaluate this endpoint because these side effects are common in pregnancy and we did not actively questioned the group receiving insulin about them. Similarly to the study of Rowan et al,[5] only 1 patient preferred to stop metformin because of the symptoms.

An important limitation of our study is the short follow-up. A longer follow-up period is needed to evaluate differences between infants of mothers treated with metformin and infants of mothers treated using insulin. This follow-up is

currently being conducted by our team but it will be several years before results are available.

In conclusion, metformin was found to provide adequate glycemic control in the majority of the patients, was associated with less weight gain and a lower frequency of neonatal hypoglycemia. In addition, a subgroup of women more likely to require supplemental insulin for adequate glycemic control was identified, a finding that might be useful when choosing a drug for the treatment of GDM. We believe that a long-term follow-up is needed, but a discussion by specialist teams on the use of metformin as a first-line drug in the treatment of patients with gestational diabetes would be of great usefulness for patients and doctors. ■

REFERENCES

1. Coustan DR, Lowe LP, Metzger BE, Dyer AR. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol 2010;202:654.e1-6.

2. Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol 2005;192:989-97.

3. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl 1):S11-63.

4. Moore LE, Briery CM, Clokey D, et al. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. J Reprod Med 2007;52:1011-5.

5. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003-15.

6. Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol 2009;113:193-205.

7. Wensel TM. Role of metformin in the treatment of gestational diabetes. Ann Pharmacother 2009;43:939-43.

8. Cheung NW. The management of gestational diabetes. Vasc Health Risk Manag 2009;5:153-64.

9. Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. Int J Gynaecol Obstet 2010;111:37-40.

10. Dhulkotia JS, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203:457.e1-9.

11. Sapienza AD, Francisco RP, Trindade TC, Zugaib M. Factors predicting the need for insulin therapy in patients with gestational diabetes mellitus. Diabetes Res Clin Pract 2010;88:81-6.

12. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl 1):S62-9.

13. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl 2):S251-60.

14. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol 2010;115:55-9.

15. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134-8.

16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 2010;1:100-7.

17. Tertti K, Ekblad U, Vahlberg T, Ronnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. Rev Diabet Stud 2008;5:95-101.

18. Tartarin P, Moison D, Guibert E, et al. Metformin exposure affects human and mouse fetal testicular cells. Hum Reprod 2012;27:3304-14.

19. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. Fert Ster 2005;83:1575-8.

20. Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care 2011;34:2279-84.