Determinants of Small for Gestational Age in Women With Type 2 Diabetes in Pregnancy: Who Should Receive Metformin?

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OBJECTIVE

In the MiTy (Metformin in Women With Type 2 Diabetes in Pregnancy) randomized trial of metformin versus placebo added to insulin, we found numerous benefits with metformin but identified an increased proportion of infants who were small for gestational age (SGA). We aimed to determine the predictors of SGA in order to individualize care.

RESEARCH DESIGN AND METHODS

Using logistic regression, we assessed baseline maternal characteristics as predictors of SGA. We compared maternal/neonatal outcomes in SGA metformin and placebo groups using the *t*, χ^2, or Fisher exact test, as appropriate.

RESULTS

Among the 502 mothers, 460 infants were eligible for this study. There were 30 infants with SGA in the metformin group (12.9%) and 15 in the placebo group (6.6%) ($P = 0.026$). Among SGA infants, those in the metformin group were delivered significantly later than those in the placebo group (37.2 vs. 35.3 weeks; $P = 0.038$). In adjusted analyses, presence of a comorbidity (chronic hypertension and/or nephropathy) (odds ratio [OR] 3.05; 95% CI 1.58–5.81) and metformin use (OR 2.26; 95% CI 1.19–4.74) were predictive of SGA. The absolute risk of SGA was much higher in women receiving metformin with comorbidity compared with women receiving metformin without comorbidity (25.0% vs. 9.8%).

CONCLUSIONS

In this study, we observed a high percentage of SGA births among women with type 2 diabetes and chronic hypertension and/or nephropathy who were treated with metformin. Therefore, with the aim of reducing SGA, it is reasonable to be cautious in our use of metformin in those with type 2 diabetes and chronic hypertension or nephropathy in pregnancy.

The incidence of type 2 diabetes in pregnancy is growing at an alarming rate (1). In a large population-based study in Ontario, Canada, the incidence of preexisting diabetes more than doubled over 14 years, from seven per 1,000 to 15 per 1,000 between 1996 and 2010 (2). In a Scottish population-based study, the incidence of type 2 diabetes in pregnancy rose by 90% between 1998 and 2013 (3). This study also found that women with type 2 diabetes in pregnancy continue to have adverse

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pregnancy outcomes, including elevated rates of preterm birth, infants large for gestational age (LGA), stillbirth, and perinatal mortality compared with women without diabetes (3). In a large audit of U.K. pregnancy clinics, women with type 2 diabetes had higher rates of perinatal death and social deprivation and were less prepared for pregnancy when compared with pregnant women with type 1 diabetes (4). They also had a higher percentage of SGA compared with women with type 1 diabetes (14.1% vs. 5.4%). The reason for this is not known.

In an effort to improve pregnancy outcomes in pregnancies complicated by type 2 diabetes, the MiTy (Metformin in Women With Type 2 Diabetes in Pregnancy) trial randomly assigned women with type 2 diabetes in pregnancy to receive metformin or placebo in addition to their usual insulin regimen (5). The MiTy trial found several maternal and neonatal benefits in the metformin group. Metformin-exposed mothers had less gestational weight gain, needed significantly less insulin during pregnancy, and had improved glycemic control, indicated by lower mean glucose and A_{1c}. Infants exposed to metformin weighed on average 200 g less, were less frequently extremely LGA (>97th percentile), less frequently had macrosomia (birth weight >4 kg), and had less adiposity, measured by sum of skinfolds and abdominal circumference. Although there was a reduction in LGA cases and adiposity measures in the metformin group, there was also an increase in the percentage of infants who were small for gestational age (SGA) (birth weight <10%) (12.9% vs. 6.6%). It is well known that SGA infants are at increased risk of mortality and adverse perinatal morbidity, such as lung disease, hypotension, necrotizing enterocolitis, poor thermoregulation, hypoglycemia, and polycythemia (6). In the long term, SGA infants are at increased risk of chronic diseases, including diabetes, cardiovascular disease, and chronic kidney disease, as well as neurodevelopmental and cognitive deficiencies, developmental delay affecting school performance, and behavioral problems (7,8).

In this study, our aim was to investigate predictors of SGA in the MiTy trial. The rationale was that if we can find groups that are more likely to have SGA infants, we can personalize the use of metformin and prescribe it to patients most likely to benefit and use it with caution in those who will not benefit or may be harmed.

RESEARCH DESIGN AND METHODS

Study Design and Population

This report involved secondary analyses of the MiTy trial, which has been previously described (5). In brief, women were eligible for the MiTy trial if they had type 2 diabetes diagnosed prior to pregnancy or in the first 20 weeks, were 18–45 years of age, were using insulin, and had a live singleton fetus between 6 and 22 weeks, 6 days gestation. Following informed consent, women were randomly assigned to receive metformin (1 g BID) or placebo added to their usual insulin regimen. Five hundred and two women were randomly assigned, 253 to metformin and 249 to placebo. This secondary analysis included women in MiTy who had liveborn infants and where the birth weight and gestational age were known.

Outcomes

SGA was defined as birth weight less than the 10th percentile for gestational age and sex, using Canadian national growth curves by Kramer et al. (9). Other neonatal outcomes included birth weight, gestational age, preterm birth <37 weeks, neonatal intensive care unit admission >24 h, neonatal hypoglycemia requiring intravenous dextrose infusion, and head and abdominal circumferences. We calculated birth weight *z* score using both the Canadian national growth curves and the gestation-related optimal weight charts, which take into account maternal ethnicity, prepregnancy BMI, parity, and neonatal sex and gestational age. In the original trial, the composite outcome included pregnancy loss (miscarriage, termination, stillbirth, or neonatal death up to 28 days), preterm birth, birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycemia, and neonatal intensive care unit admission lasting >24 h. In this post hoc analysis, we included only live births; therefore, pregnancy loss was eliminated from the composite outcome. Given that there is some evidence that those infants below the fifth centile have worse outcomes (10,11), we also looked at infants in the ≤5th percentile. Diabetic nephropathy in the original MiTy trial was defined as albuminuria/proteinuria and/or renal dysfunction secondary to diabetes based on the information obtained at enrollment (5). MiTy participants were recruited and treated at centers in Canada and Australia. Based on Diabetes Canada clinical practice guidelines, the definition of nephropathy is urine albumin/creatinine ratio >2 mg/mmol or 24-h urine collection for albumin >30 mg/day. In Diabetes Australia clinical practice guidelines, it is defined as albumin/creatinine ratio >2.5 mg/mmol in males and >3.5 mg/mmol in females or 24-h urine collection for albumin >30 mg/day. It is worth noting that in the MiTy study, women were excluded from participation if they had serum creatinine >130 μmol/L or creatinine clearance <60 mL/min (5).

Statistical Analysis

Maternal baseline characteristics were summarized, first in all women according to SGA status of their infants, and second in women who had SGA infants according to metformin treatment group. Maternal and neonatal outcomes were summarized in the SGA infant subset according to metformin treatment group. Summaries used means and SDs or medians with interquartile ranges for continuous variables and counts and percentages for categorical variables. Comparisons between groups used the *t* (where means are presented), Wilcoxon rank sum (where medians are presented), and χ^2 or Fisher exact test for categorical variables, as appropriate.

Given the relatively small absolute number of SGA infants, our investigation of predictors of SGA began with specification of a small set of candidate variables available early in pregnancy, chosen independently of the results of the comparisons described above: maternal prepregnancy BMI, chronic hypertension, diabetic nephropathy, smoking during pregnancy, baseline HbA_{1c}, and metformin. We used univariate logistic regression analyses to estimate the odds ratio (OR) for each variable and fitted a multiple regression model with all variables. Variables with no clear relationship to SGA were removed on the basis of their large *P* values ($P \geq 0.2$). To simplify the presentation here, and because of the small number of women with

diabetic nephropathy alone, we formed a comorbidity variable denoting the presence of chronic hypertension or diabetic nephropathy. We referred to this group as those with comorbidity. Model 2 added later pregnancy characteristics, such as HbA_{1c} at 34–36 weeks' gestation and weight gain under the Institute of Medicine (IOM) criteria, as potential predictors of SGA, keeping in mind that both variables are potentially affected by metformin treatment.

Finally, the effect of adding metformin treatment on the risks of SGA and LGA was assessed in women with and without comorbidity. We calculated the number needed to treat with metformin to reduce LGA and number needed to treat with metformin per additional case of SGA in each group as the reciprocals of the absolute risk difference in each comorbidity group.

Ethics

Ethical approval for the MiTy trial was obtained at each of the participating sites. This secondary analysis of the MiTy trial was approved by the Mount Sinai Hospital Ethics Board (Toronto, Ontario, Canada).

RESULTS

Of the 502 participants randomly assigned in MiTy, 14 women withdrew, six were lost to follow-up, and 21 experienced pregnancy loss. There was one infant in whom SGA could not be determined from the growth charts, because the gestational age at birth was too low. Therefore, in this secondary analysis, we included the outcomes from 460 infants, 232 whose mothers who received metformin and 228 whose mothers received placebo. In total, there were 45 infants with SGA: 30 infants with SGA in the metformin group (12.9%) and 15 infants with SGA in the placebo group (6.6%). Of these, 21 (70%) of 30 in the metformin group were below the fifth centile for weight, whereas 10 (66%) of 15 were above the fifth centile in the placebo group.

Baseline Characteristics

The maternal baseline characteristics were generally similar between the mothers without SGA infants and those with SGA infants, with the exception of chronic hypertension and diabetic nephropathy, which were significantly more common in the mothers who gave birth to SGA infants (chronic hypertension 37.8% vs. 16.6% with SGA; P = 0.001 and diabetic nephropathy 15.6% vs. 5.3% with SGA; P = 0.018) (Table 1). Among those women with SGA infants, the 30 women in the metformin group had lower first HbA_{1c} levels in pregnancy (6.9% vs. 7.9%; P = 0.026) and lower HbA_{1c} levels at entry (6.1% vs. 6.7%; P = 0.024) than the 15 women in the SGA placebo group (Table 2).

Maternal and Neonatal Outcomes

Among SGA infants, those in the metformin group were delivered significantly later than those in the placebo group (37.24 vs. 35.3 weeks; P = 0.038) (Supplementary Fig. 3). There was no statistically significant difference in the other outcomes (Table 3).

Among those 31 infants (metformin n = 21; placebo n = 10) below the fifth centile in weight using the Canadian national growth curves (9), infants in the metformin group experienced fewer adverse neonatal composite outcomes than those in the placebo group (33.3% vs. 80.0%; P = 0.041) (Supplementary Table 1).

In univariate logistic regression models assessing chronic hypertension, nephropathy, metformin, prepregnancy BMI, smoking, and first HbA_{1c} in pregnancy, only the comorbid conditions (chronic hypertension and nephropathy) and metformin use were statistically significant predictors of SGA (Supplementary Table 2). Although the SGA metformin group had lower HbA_{1c} levels at entry, HbA_{1c} at entry was not predictive of SGA (OR 1.02; 95% CI 0.84–1.22; P = 0.815). In a multivariate model containing the variables nephropathy, chronic hypertension, and metformin, all three were statistically significant and had ORs similar to those in the univariate models (Supplementary Table 2). In the model with a comorbidity variable based on the presence of chronic hypertension or nephropathy, both metformin use (OR 2.26; 95% CI 1.19–4.47) and the comorbidity variable (OR 3.05; 95% CI 1.58–5.81) were strongly associated with SGA. There was no evidence of an interaction between metformin and the comorbidity variable (OR for interaction 1.02; P = 0.975) (Supplementary Table 2). When we combined these comorbidities and added late pregnancy factors, such as last HbA_{1c} (at 34–36 weeks' gestation) and weight gain below the IOM criteria, we found that comorbidity and last HbA_{1c} at 34–36 weeks were independent predictors of SGA (Supplementary Table 3).

Given that lower HbA_{1c} at 34–36 weeks predicted higher risk of SGA, we sought to determine if there was a difference in the mean glucose between mothers of the SGA, LGA, and appropriately grown (AGA) infants, both over the entire pregnancy and in each trimester. We found that mean glucose levels over the whole pregnancy and in each trimester were different across the three groups, with the lowest being in the SGA group (Supplementary Table 4*A*). When comparing mean glucose levels across trimesters in the SGA metformin versus SGA placebo groups, glucose levels, although lower in the metformin group, were not significantly different (Supplementary Table 4*B*). Mean glucose was unchanged throughout pregnancy in women taking metformin who had SGA babies; however, it dropped in the third trimester in women receiving placebo who had SGA babies (Supplementary Table 4*B* and Supplementary Fig. 1).

Using metformin and presence of comorbidities for predicting SGA, the area under the receiver operating characteristic curve was 0.67. As noted above, there was no evidence for a different relative effect of metformin on the risk of SGA in those with and without comorbidity (hypertension/nephropathy). However, the relative effect of metformin has different consequences when the baseline risk varies. In the placebo group, the absolute risk of SGA was higher in women with comorbidity (12.7%) than in women without (4.6%). The effect of metformin use amplified these baseline differences, so the absolute observed risk of SGA during metformin use was much higher in those with comorbidity (25.0%) than in those without (9.8%). Figure 1 shows the distribution of birth weight z scores when metformin or placebo was added in women with and without comorbidity. The birth weight z score was similar in those without comorbidity using metformin and those with comorbidity but without metformin. The birth weight z score was smallest in those with both metformin use and comorbidity.

Finally, we compared the risks of SGA, LGA, and the composite outcome,

Table 1—Baseline characteristics in all women, women with SGA infants, and those without SGA infants

	Overall	No SGA	SGA	*P**
N of patients	460	415	45	
Age (years), mean (SD)	34.9 (4.8)	34.8 (4.8)	35.8 (4.5)	0.188
Non-European, *n* (%)	364 (79.1)	323 (77.8)	41 (91.1)	0.059
Parity, median (IQR)	2 (1, 3)	2 (1, 3)	1 (0, 3)	0.790
Prepregnancy BMI (kg/m^2), mean (SD)	33.8 (7.3)	33.9 (7.4)	32.4 (6.4)	0.200
Total weight gain during pregnancy, *n* (%)				0.392
Below IoM guidelines	89 (19.7)	77 (18.9)	12 (27.3)	
Within IoM guidelines	114 (25.3)	103 (25.3)	11 (25.0)	
Above IoM guidelines	248 (55.0)	227 (55.8)	21 (47.7)	
Family history of diabetes, *n* (%)	383 (83.3)	345 (83.1)	38 (84.4)	0.989
Insulin (units/kg/day), mean (SD)	0.66 (0.52)	0.67 (0.52)	0.64 (0.51)	0.745
Gestational age at random assignment (weeks), mean (SD)	16.5 (3.8)	16.6 (3.7)	15.9 (4.0)	0.258
First HbA_{1c} in pregnancy, mean (SD)				0.815
%	7.18 (1.68)	7.17 (1.71)	7.23 (1.38)	
mmol/mol	54.9 (18.3)	54.9 (18.7)	55.6 (15.1)	
HbA_{1c} at entry, mean (SD)				0.711
%	6.37 (1.16)	6.38 (1.20)	6.30 (0.69)	
mmol/mol	46.1 (12.6)	46.2 (13.1)	45.4 (7.5)	
Nephropathy, *n* (%)	**29 (6.3)**	**22 (5.3)**	**7 (15.6)**	**0.018**
Chronic hypertension, *n* (%)	**86 (18.7)**	**69 (16.6)**	**17 (37.8)**	**0.001**
Smoking status, *n* (%)				0.393
Never smoked	346 (75.2)	308 (74.2)	38 (84.4)	
Smoked before only	64 (13.9)	60 (14.5)	4 (8.9)	
Smoked during pregnancy but stopped	19 (4.1)	17 (4.1)	2 (4.4)	
Smoked during pregnancy and continued	31 (6.7)	30 (7.2)	1 (2.2)	
Low SES variable, *n* (%)†	192 (41.7)	178 (42.9)	13 (31.1)	0.173
Metformin use in first trimester, *n* (%)	285 (62.0)	258 (62.2)	27 (60.0)	0.902
Treated with metformin during trial, *n* (%)	**232 (50.4)**	**202 (48.7)**	**30 (66.7)**	**0.033**

Bold font indicates significance. IQR, interquartile range; SES, socioeconomic. **P* value compares SGA and non-SGA groups. †Met any of the following criteria: immigrated to Canada or Australia within 5 years of study entry, marital status was single, or highest attained education was secondary school or less.

with and without metformin, in those with and without comorbidity, in an attempt to quantify both the potential harms and benefits of adding metformin in the two groups. We found that, in pregnant women with type 2 diabetes without comorbidity, adding metformin decreased LGA by 7% (24.5% vs. 31.2%) but increased SGA by 5% (9.8% vs. 4.6%) and increased the composite outcome by 1% (33.3% vs. 32.0%). In women with type 2 diabetes and comorbidity, adding metformin decreased LGA by a similar amount, 8% (20.8% vs. 29.1%), but increased SGA by 12% (25.0% vs. 12.7%) and increased the composite outcome by 8% (56.2% vs. 48.1%) (Supplementary Fig. 2 and Table 4). Therefore, the number needed to treat with metformin to avoid a case of LGA is similar in both groups (12 with comorbidity vs. 15 without), but the number needed to treat with metformin per additional case of SGA is much lower in women with comorbidity (8 vs. 19, respectively).

CONCLUSIONS

We found that in our cohort of women with type 2 diabetes in the MiTy trial, mothers with chronic hypertension and diabetic nephropathy had more SGA infants. SGA infants in the metformin group were delivered significantly later than the SGA infants in the placebo group. In those below the fifth centile in weight, SGA infants in the metformin group had a lower rate of the adverse neonatal composite outcome compared with SGA infants in the placebo group. Early pregnancy predictors of developing SGA were presence of chronic hypertension and/or nephropathy at baseline and treatment with metformin; lower HbA_{1c} in the third trimester was also associated with SGA. In those receiving metformin, the numbers needed to treat with metformin per avoided case of LGA were similar in women with and without chronic hypertension and/or nephropathy, but the number needed to treat with metformin per additional case of SGA was considerably lower in those with comorbidity.

We found that mothers with chronic hypertension and/or nephropathy had a higher risk of SGA than those without hypertension/nephropathy, and this risk was even higher with metformin use: one quarter of all women with comorbidity taking metformin had an SGA

Table 2—Baseline characteristics between those in the metformin group who delivered SGA infants and those in the placebo group who delivered SGA infants

	SGA metformin	SGA placebo	*P*
N of patients	30	15	
Age (years), mean (SD)	36.1 (4.1)	35.2 (5.2)	0.508
Non-European, *n* (%)	27 (90.0)	14 (93.3)	1.00
Parity, median (IQR)	1 (1, 3)	2 (0, 3)	0.912
Prepregnancy BMI (kg/m^2), mean (SD)	33.1 (6.1)	31.1 (6.8)	0.326
Family history of diabetes, *n* (%)	24 (80.0)	14 (93.3)	0.467
Insulin (units/kg/day), mean (SD)	0.60 (0.54)	0.72 (0.48)	0.435
Gestational age at random assignment (weeks), mean (SD)	16.5 (4.2)	14.6 (3.3)	0.133
First HbA_{1c} in pregnancy, mean (SD)			**0.026**
%	**6.91 (1.01)**	**7.90 (1.80)**	
mmol/mol	**52.0 (11.0)**	**62.8 (19.7)**	
HbA_{1c} at entry, mean (SD)			**0.024**
%	**6.13 (0.60)**	**6.67 (0.75)**	
mmol/mol	**43.6 (6.5)**	**49.4 (8.2)**	
Nephropathy, *n* (%)	3 (10.0)	4 (26.7)	0.309
Chronic hypertension, *n* (%)	11 (36.7)	6 (40.0)	1.00
Smoking status, *n* (%)			0.197
Never smoked	26 (86.7)	12 (80.0)	
Smoked before only	1 (3.3)	3 (20.0)	
Smoked during pregnancy but stopped	2 (6.7)	0 (0.0)	
Smoked during pregnancy and continued	1 (3.3)	0 (0.0)	
Low SES variable*	9 (30.0)	5 (33.3)	1.00
Metformin use in first trimester, *n* (%)	18 (60.0)	9 (60.0)	1.00

Bold font indicates significance. IQR, interquartile range; SES, socioeconomic. *Met any of the following criteria: immigrated to Canada or Australia within 5 years of study entry, marital status was single, or highest attained education was secondary school or less.

Table 3—Maternal and neonatal outcomes in the metformin group who delivered SGA infants and those in the placebo group who delivered SGA infants

	SGA metformin	SGA placebo	*P*
N of patients	30	15	
Maternal outcomes			
Preeclampsia, *n* (%)	11 (36.7)	7 (46.7)	0.747
Worsening chronic hypertension, *n* (%)	5 (16.7)	4 (26.7)	0.693
Cesarean section, *n* (%)	17 (56.7)	12 (80.0)	0.226
Insulin (units/kg/day) at 34–36 weeks GA, median (IQR)	0.71 (0.49, 1.22)	1.20 (0.84, 1.94)	0.116
Neonatal outcomes			
GA (weeks), mean (SD)	**37.2 (2.3)**	**35.3 (3.7)**	**0.038**
Birth weight (g), mean (SD)	2,285 (484)	1,943 (748)	0.070
Birth weight *z* score, mean (SD)*	−1.21 (0.62)	−1.65 (0.95)	0.070
GROW birth weight *z* score†	−2.19 (0.68)	−2.39 (1.01)	0.429
Sum of skinfolds, median (IQR)	12.4 (10.3, 14.2)	13.7 (12.7, 18.2)	0.113
Head circumference (cm), mean (SD)	31.9 (2.9)	30.4 (3.4)	0.158
Abdominal circumference (cm), mean (SD)	29.1 (2.7)	29.2 (3.5)	0.979
Composite outcome present, *n* (%)‡	11 (36.7)	10 (66.7)	0.113
Preterm birth, *n* (%)	8 (26.7)	8 (53.3)	0.152
NICU admission >24 h, *n* (%)	7 (23.3)	7 (50.0)	0.155
Neonatal hypoglycemia, *n* (%)	4 (13.8)	5 (38.5)	0.163

Bold font indicates significance. GA, gestational age; GROW, gestation-related optimal weight; IQR, interquartile range; NICU, neonatal intensive care unit. *Using Kramer growth curves (9). †Using GROW growth charts that adjust infant birth weight for maternal parity, ethnicity, height, and weight and for infant sex and gestational age (24). ‡Composite outcome includes preterm birth, birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycemia, and NICU admission lasting >24 h.

Table 4—Change in outcomes when metformin was added in those with and without chronic hypertension and/or nephropathy

Outcome	With chronic hypertension/nephropathy	Without chronic hypertension/nephropathy
LGA (%)		
Without metformin	29.1	31.2
With metformin	20.8	24.5
Decrease	8	7
SGA (%)		
Without metformin	12.7	4.6
With metformin	25.0	9.8
Increase	12	5
Composite outcome present (%)		
Without metformin	48.1	32.0
With metformin	56.2	33.3
Increase	8	1

infant. This is noteworthy because of the increasing incidence of chronic hypertension seen in women with diabetes in pregnancy. One study found the incidence of chronic hypertension in women with preexisting diabetes (type 1 and type 2 diabetes) increased from 4% in 1995 to 14% in 2008 (12). Many studies have shown that chronic hypertension in pregnancy is associated with adverse pregnancy outcomes, including increased rates of preterm delivery, preeclampsia, SGA, and perinatal death (12–15). Few studies have examined the effect of chronic hypertension in women with preexisting diabetes on SGA. In a retrospective cohort study in California, the incidence of SGA was 9.7% in women with preexisting diabetes and no chronic hypertension but 18.2% in those with diabetes and chronic hypertension (16). In contrast, in our study, SGA was 4.6% without comorbidity but 12.7% with comorbidity. Adding metformin in this cohort increased the risk of SGA to 25.0%, thus giving the highest rate of SGA. While looking at the possible tradeoffs, we found that while the number needed to treat with metformin to avoid a case of LGA was similar in women with and without chronic hypertension and/or nephropathy, the number needed to treat with metformin per additional case of SGA was lower in those with these comorbidities. Given the potential to increase SGA in a population already prone to SGA, it may be prudent to use metformin with caution in this population of women with type 2 diabetes and comorbidity and weigh the risks and benefits. Unfortunately, withholding metformin in this group will also prevent them from reaping the other benefits noted in the MiTy trial, including improved glycemic control, reduction in maternal weight gain, fewer cesarean sections, and lower insulin doses (5).

SGA infants in the metformin group were delivered significantly later than the SGA infants in the placebo group, and they had a lower rate of the adverse neonatal composite outcome. This was likely driven by their later delivery. This finding is not surprising, because we showed in the MiTy trial that the birth weight *z* score distribution of the whole metformin group was shifted to the left; therefore, the whole group weighed less (5). We hypothesize that some infants who had moved down to the SGA cutoff were simply smaller but did not experience the same amount of preterm birth or morbidity. Given that the absolute number of SGA infants was small here, further research is needed to confirm this hypothesis.

We found that weight gain below the IOM recommendations was not a predictor of SGA in our cohort. Although weight gain below the IOM recommendations has been associated with SGA in other populations (17,18), this has not been a consistent finding (19). Our findings are consistent with those of another study in obese women with type

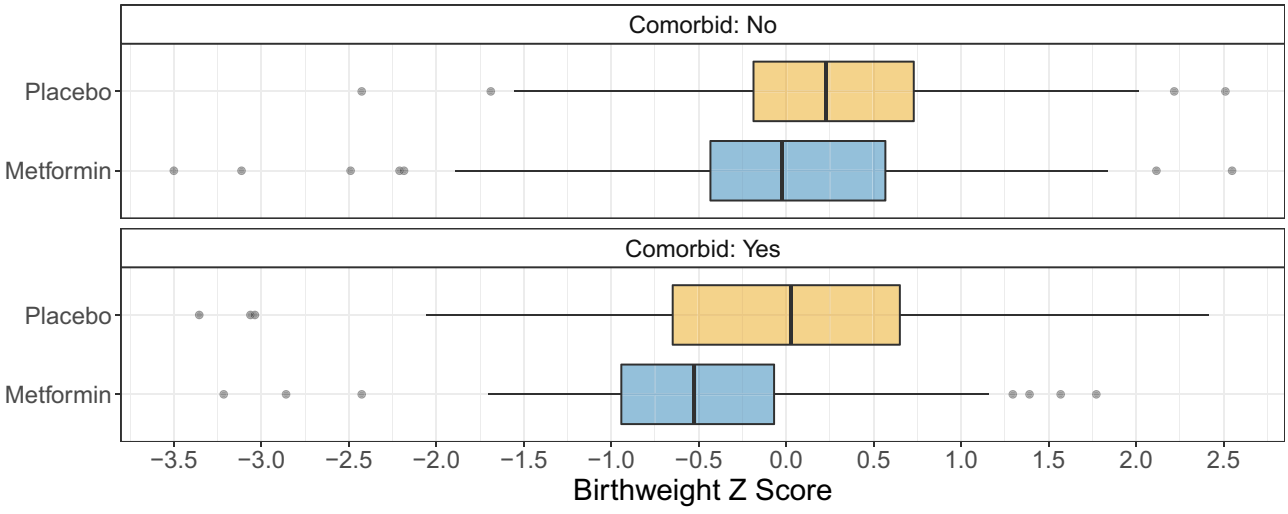

Figure 1—Boxplots of birthweight z-scores as measured by Kramer growth curves (9), when metformin or placebo is added to women with and without comorbidity (chronic hypertension and/or nephropathy).

2 diabetes, which showed that weight gain of ≤5 kg did not result in higher rates of SGA but in fact was associated with improved outcomes, such as fewer LGA infants, more infants who were delivered closer to term, and more infants who had lower rates of perinatal morbidity compared with those who gained >5 kg during pregnancy (20). These women also required less insulin. The investigators hypothesized that the reduced maternal weight gain led to reduced insulin resistance and therefore better outcomes. Cigarette smoking in this study was also not a predictor of SGA, possibly secondary to the small number of participants who smoked during pregnancy.

In our study, a lower final HbA_{1c} at 34 weeks' gestation was associated with SGA. Few studies have associated tight glycemic control with SGA. In a cohort of 5,271 Portuguese women from the National Registry of Gestational Diabetes, mothers of infants with SGA had a small but significant difference in HbA_{1c} (5.18% with SGA infants vs. 5.25% without) (17). In a cohort of 1,500 pregnant women in China undergoing gestational diabetes screening, low glucose levels were associated with increased risk of SGA (21). In a study by Langer et al., investigators found an increased SGA rate in women with gestational diabetes who had a mean glucose level <86 mg/dL (4.8 mmol/L). The mean glucose in our SGA infants (106 mg/dL or 5.89 mmol/L) was lower but not significantly different than that in the AGA cohort (109 mg/dL or 6.04 mmol/L) and was higher than that found in the Langer et al. study. However, their population was women with gestational diabetes compared with women with type 2 diabetes in our study, where the relationship may be different. While the mean glucose level was significantly different across the LGA, AGA, and SGA groups (Supplementary Table 4*A*), the SGA and AGA mean glucose levels seem more similar to each other, with the most different being the mean glucose in the mothers of LGA infants. Although the metformin SGA babies had a lower mean glucose than the placebo SGA mean glucose at all trimesters (lowest glucose 103 mg/dL or 5.74 mmol/L) (Supplementary Table 4*B*), they were not statistically significantly different, and the glucose levels were considerably higher than the mean glucose found in normal pregnancies of 88 mg/dL or 4.8 mmol/L (22). It is interesting to note that while the mean glucose was unchanged throughout pregnancy in women receiving metformin who had SGA babies, it dropped in the third trimester in women receiving placebo. Such a drop may be a reflection of placental insufficiency, which can be reflected by dropping glucose levels (23). More studies are needed to understand the relationship between low glucose and SGA.

This analysis has many strengths. The data were derived from a well-described cohort and prospectively collected. This was a secondary analysis from a randomized double-masked placebo-controlled trial, so there was no confounding of metformin treatment by indication. Where there were imbalances at baseline, we tried to adjust for them. We acknowledge, however, that there are some limitations. This was a post hoc analysis of an unexpected finding in the MiTy trial. The number of SGA babies was small, and therefore, extensive adjustment for potential confounders, regardless of baseline differences, and data-based identification of other predictors were not feasible.

In this study, pregnant women with type 2 diabetes and comorbidity (chronic hypertension and/or nephropathy) receiving metformin, despite numerous benefits, gave birth to more SGA infants compared with those not receiving metformin. Their numbers needed to treat to avoid a case of LGA were similar to those among women without comorbidity, but their numbers needed to treat per additional case of SGA were lower. Both LGA and SGA have potential harms associated harms, and it is difficult to say which is worse: not using metformin to reduce LGA in order to prevent SGA, or using metformin to reduce LGA while at the same time increasing the potential for SGA. However, given that the risk of SGA is so high (25%) in those with comorbidity and metformin use, until there is further evidence to confirm or refute these findings, it is reasonable to use a cautious approach and use metformin judiciously in those with type 2 diabetes and chronic hypertension or nephropathy.

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Author Contributions. All authors designed the study, contributed to interpretation of the data, and reviewed and provided critical revisions to the manuscript. D.S.F., G.T., and K.E.M. designed the statistical analysis plan. D.S.F. and K.E.M. wrote the first draft of the manuscript. G.T. performed the statistical analyses. D.S.F. and K.E.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

APPENDIX

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