Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial

*Denice S Feig, Lois E Donovan, Bernard Zinman, J J Sanchez, Elizabeth Asztalos, Edmond A Ryan, I G Fantus, Eileen Hutton, Anthony B Armson, Lorraine L Lipscombe, David Simmons, Jon F R Barrett, Paul J Karanicolas, Siobhan Tobin, H David McIntyre, Simon Yu Tian, George Tomlinson, and Kellie E Murphy, on behalf of the MiTy Collaborative Group**

Lancet Diabetes Endocrinol 2020; 8: 834–44

See **Comment** page 802

*A list of collaborators in the MiTy trial is provided in the appendix (pp 4–10)

Department of Medicine, University of Toronto, Toronto, ON, Canada (Prof D S Feig MD, B Zinman MD, I G Fantus MD, L L Lipscombe MD, G Tomlinson PhD, K E Murphy MD); **Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada** (Prof D S Feig, B Zinman, I G Fantus, K E Murphy); **Sinai Health System, Mount Sinai Hospital, Toronto, ON, Canada** (Prof D S Feig, B Zinman, I G Fantus, K E Murphy); **Cumming School of Medicine, Department of Medicine, Department of Obstetrics and Gynecology, University of Calgary, Calgary, AB, Canada** (L E Donovan MD); **Alberta Children's Hospital Research Institute, Calgary, AB, Canada** (L E Donovan); **Sunnybrook Research Institute, Toronto, ON, Canada** (J J Sanchez PhD, J F R Barrett MD, P J Karanicolas MD, S Tobin HBSc, S Y Tian PhD); **Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (E Asztalos MD, J F R Barrett, P J Karanicolas); **University of Alberta, Edmonton, AB, Canada** (E A Ryan MD); **McMaster University Hamilton, ON, Canada** (E Hutton PhD); **Dalhousie University, Halifax, NS, Canada** (A B Armson MD); **Women's College Hospital, Toronto, ON, Canada** (L L Lipscombe); **Western Sydney University, Sydney, NSW, Australia** (D Simmons MD); **Mater Research, University of Queensland, South Brisbane, QLD, Australia** (H D McIntyre MD); **Department of Medicine, University Health**

Summary

Background Although metformin is increasingly being used in women with type 2 diabetes during pregnancy, little data exist on the benefits and harms of metformin use on pregnancy outcomes in these women. We aimed to investigate the effects of the addition of metformin to a standard regimen of insulin on neonatal morbidity and mortality in pregnant women with type 2 diabetes.

Methods In this prospective, multicentre, international, randomised, parallel, double-masked, placebo-controlled trial, women with type 2 diabetes during pregnancy were randomly assigned from 25 centres in Canada and four in Australia to receive either metformin 1000 mg twice daily or placebo, added to insulin. Randomisation was done via a web-based computerised randomisation service and stratified by centre and pre-pregnancy BMI (<30 kg/m² or ≥30 kg/m²) in a ratio of 1:1 using random block sizes of 4 and 6. Women were eligible if they had type 2 diabetes, were on insulin, had a singleton viable pregnancy, and were between 6 and 22 weeks plus 6 days' gestation. Participants were asked to check their fasting blood glucose level before the first meal of the day, before the last meal of the day, and 2 h after each meal. Insulin doses were adjusted aiming for identical glucose targets (fasting glucose <5·3 mmol/L [95 mg/dL], 2-h postprandial glucose <6·7 mmol/L [120 mg/dL]). Study visits were done monthly and patients were seen every 1–4 weeks as was needed for standard clinical care. At study visits blood pressure and bodyweight were measured; patients were asked about tolerance to their pills, any hospitalisations, insulin doses, and severe hypoglycaemia events; and glucometer readings were downloaded to the central coordinating centre. Participants, caregivers, and outcome assessors were masked to the intervention. The primary outcome was a composite of fetal and neonatal outcomes, for which we calculated the relative risk and 95% CI between groups, stratifying by site and BMI using a log-binomial regression model with an intention-to-treat analysis. Secondary outcomes included several relevant maternal and neonatal outcomes. The trial was registered with ClinicalTrials.gov, NCT01353391.

Findings Between May 25, 2011, and Oct 11, 2018, we randomly assigned 502 women, 253 (50%) to metformin and 249 (50%) to placebo. Complete data were available for 233 (92%) participants in the metformin group and 240 (96%) in the placebo group for the primary outcome. We found no significant difference in the primary composite neonatal outcome between the two groups (40% *vs* 40%; p=0·86; relative risk [RR] 1·02 [0·83 to 1·26]). Compared with women in the placebo group, metformin-treated women achieved better glycaemic control (HbA_{1c} at 34 weeks' gestation 41·0 mmol/mol [SD 8·5] *vs* 43·2 mmol/mol [–10]; 5·90% *vs* 6·10%; p=0·015; mean glucose 6·05 [0·93] *vs* 6·27 [0·90]; difference –0·2 [–0·4 to 0·0]), required less insulin (1·1 units per kg per day *vs* 1·5 units per kg per day; difference –0·4 [95% CI –0·5 to –0·2]; p<0·0001), gained less weight (7·2 kg *vs* 9·0 kg; difference –1·8 [–2·7 to –0·9]; p<0·0001) and had fewer caesarean births (125 [53%] of 234 in the metformin group *vs* 148 [63%] of 236 in the placebo group; relative risk [RR] 0·85 [95% CI 0·73 to 0·99]; p=0·031). We found no significant difference between the groups in hypertensive disorders (55 [23%] in the metformin group *vs* 56 [23%] in the placebo group; p=0·93; RR 0·99 [0·72 to 1·35]). Compared with those in the placebo group, metformin-exposed infants weighed less (mean birthweight 3156 g [SD 742] *vs* 3375 g [742]; difference –218 [–353 to –82]; p=0·002), fewer were above the 97th centile for birthweight (20 [9%] in the metformin group *vs* 34 [15%] in the placebo group; RR 0·58 [0·34 to 0·97]; p=0·041), fewer weighed 4000 g or more at birth (28 [12%] in the metformin group *vs* 44 [19%] in the placebo group; RR 0·65 [0·43 to 0·99]; p=0·046), and metformin-exposed infants had reduced adiposity measures (mean sum of skinfolds 16·0 mm [SD 5·0] *vs* 17·4 [6·2] mm; difference –1·41 [–2·6 to –0·2]; p=0·024; mean neonatal fat mass 13·2 [SD 6·2] *vs* 14·6 [5·0]; p=0·017). 30 (13%) infants in the metformin group and 15 (7%) in the placebo group were small for gestational age (RR 1·96 [1·10 to 3·64]; p=0·026). We found no significant difference in the cord c-peptide between groups (673 pmol/L [435] in the metformin group *vs* 758 pmol/L [595] in the placebo group; p=0·10; ratio of means 0·88 [0·72 to 1·02]). The most common adverse event reported was gastrointestinal (38 events in the metformin group and 38 events in the placebo group).

Interpretation We found several maternal glycaemic and neonatal adiposity benefits in the metformin group. Along with reduced maternal weight gain and insulin dosage and improved glycaemic control, the lower adiposity and

infant size measurements resulted in fewer large infants but a higher proportion of small-for-gestational-age infants. Understanding the implications of these effects on infants will be important to properly advise patients who are contemplating the use of metformin during pregnancy.

Funding Canadian Institutes of Health Research, Lunenfeld-Tanenbaum Research Institute, University of Toronto.

Network, Toronto, ON, Canada (G Tomlinson)**; and Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada** (K E Murphy)

Correspondence to:
Professor Denice S Feig, Mount Sinai Hospital, Toronto, ON, M5T 3L9, Canada
d.feig@utoronto.ca

See **Online** for appendix

Introduction

In the past 20 years, the prevalence of type 2 diabetes in pregnancy has more than doubled,[1] driven primarily by a younger age of onset[2] and by an increasing prevalence of maternal obesity.[3] Pregnant women with type 2 diabetes are often from Black, Hispanic, Asian, and Indigenous ethnic groups; typically have overweight or obesity; and are often economically disadvantaged.[4] Pregnant women with type 2 diabetes are at high risk for adverse pregnancy outcomes including increased rates of pre-eclampsia and caesarean section in mothers, and congenital anomalies, perinatal mortality, preterm birth, being large for gestational age, and neonatal intensive care unit (NICU) admissions in infants,[1,4] and achieving optimal glucose control is challenging.[4] These women often require high insulin doses,[5] which are uncomfortable, costly, and associated with increased gestational weight gain, which might further contribute to large-for-gestational-age infants and increased perinatal morbidity.[3] Thus, an urgent unmet need exists to identify the optimal management for this at-risk population.

Metformin is a biguanide, which is commonly used as first-line therapy in the management of type 2 diabetes, but the drug's role during pregnancy remains controversial.[6] Potential theoretical benefits include reduction in glucose and insulin resistance, lowered insulin requirements, and reduced maternal weight gain. Metformin crosses the placenta[7] and might also lower glucose and insulin resistance in the fetus, leading to reductions in the number of infants who are large for gestational age and other fetal morbidities, such as neonatal hypoglycaemia[8] and respiratory distress syndrome, and pregnancy loss. However, because fetal metformin concentrations are similar or higher than those in the mother,[7] potential safety concerns exist. Some studies of women with gestational diabetes have found increased overweight or obesity in metformin-exposed children.[9] Pregnant women with type 2 diabetes are increasingly prescribed metformin despite insufficient knowledge of the drug's short-term and long-term effects.[10]

Five small studies of metformin use in women with type 2 diabetes in pregnancy have been reported,[11–15] with

Research in context

Evidence before this study

We searched MEDLINE for articles published before March 7, 2020, with no language restrictions. We used the search terms "diabetes mellitus or diabetes" AND, "pregnancy" OR "pregnancy in diabetics", AND "metformin" AND "randomized controlled trial". We identified five small studies, two of which examined neonatal outcomes. One study showed reduced maternal hypoglycaemia, neonatal hypoglycaemia, and neonatal intensive care unit (NICU) admissions in the metformin group, and the other showed reduced pregnancy-induced hypertension, gestational weight gain, neonatal hypoglycaemia, and NICU admissions. However, these studies were limited by methodological issues, including small sample sizes, insufficient appropriate allocation assignment, masking, and intention-to-treat analysis. Thus, little evidence exists to guide clinicians on the use of metformin as an adjunct to insulin in women with type 2 diabetes in pregnancy.

Added value of this study

To our knowledge, this is the first large, adequately powered, multicentre, international, double-masked, placebo-controlled trial in women with type 2 diabetes during pregnancy, randomly assigned to the addition of metformin or placebo to their standard regimen of insulin. We found no significant difference between groups in the primary composite outcome of neonatal mortality and serious morbidity. However, compared with those in the placebo group, metformin-treated women and their infants had several benefits, including better glycaemic control, lower insulin requirements, less gestational weight gain, and fewer caesarean births. Compared with those in the placebo group, infants of mothers taking metformin weighed an average of 210 g less, were less likely to be extremely large for gestational age and to weigh 4000 g or more at birth, and had reduced adiposity measures. More infants were, however, small for gestational age in the metformin group than in the placebo group.

Implications of all the available evidence

Although we found no significant difference in a composite of serious neonatal outcomes in women with type 2 diabetes treated with metformin or placebo added to insulin, secondary analysis several maternal glycaemic and neonatal adiposity benefits in the metformin group. The lower adiposity and infant size measurements resulted in fewer large infants but a higher proportion of small-for-gestational-age infants. Understanding the implications of these effects on infants will be important to properly advise women who are contemplating the use of metformin during pregnancy. Longer term surveillance of these infants is essential to investigate the significance of these findings.

two reporting neonatal outcomes.[11,12] One study showed reduced maternal hypoglycaemia, neonatal hypoglycaemia, and NICU admissions in the metformin group,[11] and the other showed reduced pregnancy-induced hypertension, gestational weight gain, neonatal hypoglycaemia, and NICU admissions.[12] These studies were limited by methodological issues, including small sample sizes and insufficient appropriate allocation assignment, masking, and intention-to-treat analysis. Thus, little evidence exists to guide clinicians on the use of metformin as an adjunct to insulin in women with type 2 diabetes in pregnancy.

The aim of the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy) trial was to investigate whether the addition of metformin to a standard regimen of insulin, would increase or decrease the risk of neonatal morbidity and mortality in pregnant women with type 2 diabetes.

Methods

Study design and participants

The MiTy trial was a multicentre, international, placebo-controlled, double-masked, randomised trial involving 29 hospital centres, 25 in Canada and four in Australia. Eligible centres had to be able to provide care to women with type 2 diabetes during pregnancy, offer care to infants who required admission to the NICU, and verify that all components of the trial could be completed.

Women were eligible if they were aged 18–45 years, diagnosed with type 2 diabetes before pregnancy or before 20 weeks' gestation (with at least two of the following: fasting glucose ≥7·0 mmol/L [126 mg/dL], ≥11·1 mmol/L [≥200 mg/dL] on a 2-h 75 g oral glucose tolerance test, or HbA_{1c} ≥48 mmol/mol [≥6·5%]),[16] receiving insulin, and had a live singleton fetus between 6 and 22 weeks plus 6 days' gestation confirmed by ultrasound. Women were initially included from 12 weeks' gestation; however, after the first three recruits the inclusion criteria were expanded to allow entry from 6 weeks because we hypothesised that longer and earlier duration of treatment might be beneficial. Women were excluded if they had type 1 diabetes, known intolerance or contraindications to metformin, or if they had previously participated in MiTy (appendix p 11). Participants were recruited when visiting their endocrinologist or obstetrician at their hospital clinic. In patients taking metformin before entering the study, the metformin was stopped before randomisation. Participants gave written informed consent.

The protocol has been previously published.[17] Participating sites and collaborators are provided in the appendix (pp 4–10). The protocol, written by the principal investigator (DSF), was approved by the steering committee, the Mount Sinai Hospital Ethics Review Board (NSP 104011), and by research ethics boards at each site.

Metformin use in MiTy was approved by Health Canada. The trial was overseen by a steering committee and done in accordance with the Declaration of Helsinki.

Randomisation and masking

Women were randomly assigned to receive either metformin or placebo in addition to a standard regimen of insulin, which usually included short-acting insulin before meals and long-acting insulin before bed. Participants, caregivers, and outcome assessors were masked to the assignment. Randomisation was done at Sunnybrook Research Institute, Toronto, ON, Canada, via a web-based computerised randomisation service and stratified by centre and pre-pregnancy body mass index (BMI; <30 or ≥30 kg/m²). Within strata, allocation was assigned in a ratio of 1:1 using random block sizes of 4 and 6.

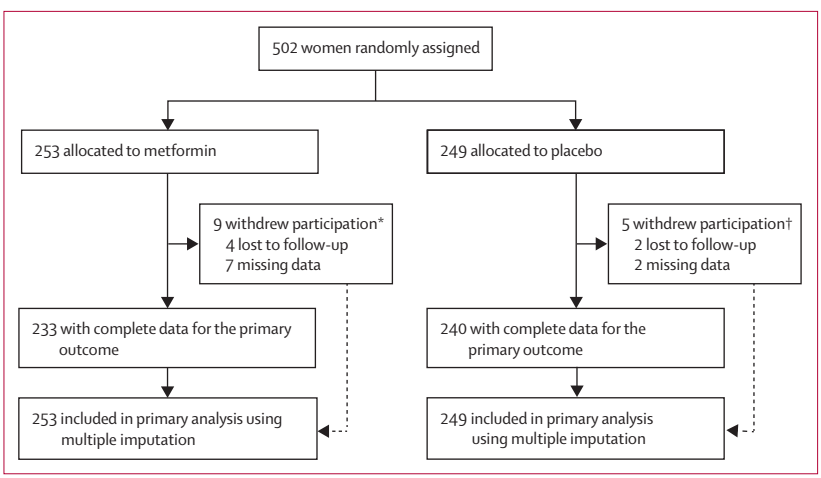

Figure 1: **Trial profile**
*Reasons included family issues (n=2); patient moved outside of study area (n=1); intervention intolerance or gastrointestinal side effects and decided to withdraw (n=1); did not want team to access medical records (n=3); not interested, bad timing, or overwhelmed (n=1); and discontinued intervention and decided to withdraw (n=1). †Reasons included intervention intolerance or gastrointestinal side effects and decided to withdraw (n=2); not interested, bad timing, overwhelmed (n=2); and discontinued intervention and decided to withdraw (n=1).

Procedures

Both groups were asked to check their fasting blood glucose level before the first meal of the day, before the last meal of the day, and 2 h after each meal. Insulin doses were adjusted aiming for identical glucose targets (fasting glucose <5·3 mmol/L [95 mg/dL], 2 h postprandial glucose <6·7 mmol/L [120 mg/dL]). Study visits were monthly for the remainder of the pregnancy. Patients were seen every 1–4 weeks as was needed for standard clinical care. At study visits, blood pressure and bodyweight were measured; patients were asked about tolerance to their pills, any hospitalisations, insulin doses, and severe hypoglycaemia events; and glucometer readings were downloaded to the central coordinating centre. Pill counts were done with each change of pill bottle to assess compliance.

To maintain masking and limit the number and severity of side-effects, metformin (500 mg) and placebo pills were gradually increased over 2 weeks to a final dose of two pills, twice daily (appendix p 33). The placebo pill was identical in appearance, taste, and consistency to

	Metformin (n=253)	Placebo (n=249)
Maternal age at randomisation, years	34·7 (5·0)	35·0 (4·6)
Age range, years	19·1–44·4	19·4–44·9
Ethnicity		
European	77 (30%)	75 (30%)
Non-European	176 (70%)	174 (70%)
Aboriginal	18 (7%)	17 (7%)
African or Caribbean origin	40 (16%)	36 (15%)
East Asian origin	26 (10%)	30 (12%)
Hispanic origin	5 (2%)	7 (3%)
Middle Eastern origin	14 (6%)	10 (4%)
Pacific Islands origin	3 (1%)	3 (1%)
South Asian	32 (13%)	48 (19%)
Multi-ethnic	14 (6%)	10 (4%)
Other	18 (7%)	11 (4%)
Unknown	6 (2%)	2 (<1%)
Previous pregnancies*	197 (78%)	199 (80%)
Gestational age at randomisation, weeks	16·5 (4·0)	16·4 (3·8)
Pre-pregnancy weight, kg†	90·5 (21·3)	90·0 (21·9)
Pre-pregnancy BMI, kg/m²	33·5 (7·1)	33·8 (7·4)
Weight at randomisation, kg	94·4 (21·4)	93·5 (21·8)
BMI at randomisation, kg/m²	35·0 (7·1)	35·2 (7·2)
BMI at randomisation ≥30 kg/m²	194 (77%)	190 (76%)
Diagnosis of type 2 diabetes before pregnancy	209 (83%)	225 (90%)
Family history of type 2 diabetes	205 (81%)	211 (85%)
Polycystic ovary syndrome	43 (17%)	45 (18%)
First HbA_{1c} during this pregnancy, mmol/mol‡	55 (17)	56 (20)
First HbA_{1c} during this pregnancy, %	7·1 (1·6)	7·3 (1·8)
HbA_{1c} concentration at randomisation, mmol/mol§	47 (13)	47 (13)
HbA_{1c} concentration at randomisation, %	6·42 (1·23)	6·41 (1·16)
Low socioeconomic status composite¶	109 (43%)	108 (43%)
Immigrated to current country‖	115/251 (46%)	117 (47%)
Immigrated within past 5 years	33/251 (13%)	31 (12%)
Self-reported risky behaviours**	45 (18%)	38 (15%)
(Continued from previous column)		
Self-reported ever smoker	29 (12%)	27 (11%)
Insulin dose at randomisation, kg per day	0·64 (0·51); 0·53 (0·24–0·83)	0·68 (0·51); 0·57 (0·26–0·90)
Presence of diabetes complications		
Retinopathy††	5 (2·0%)	8 (3·2%)
Nephropathy	11 (4·3%)	19 (7·6%)
Hypertension‡‡	45 (17·8%)	48 (19·3%)
Chronic hypertension	44 (17·4%)	48 (19·3%)
Blood pressure§§		
Systolic (mm Hg)	119·2 (13·3)	118·8 (13·5)
Diastolic (mm Hg)	72·3 (9·4)	73·0 (9·3)
Metformin used before pregnancy within past 12 months	170 (67%)	171 (69%)
Metformin used during first trimester	160 (63%)	148 (59%)

Data are mean (SD), n (%), or median (IQR). *In the metformin group 171 (68%) women had 1–4 previous pregnancies and 26 (10%) women had >4 previous pregnancies. In the placebo group 168 (68%) women had 1–4 previous pregnancies and 31 (12%) women had >4 previous pregnancies. †One (<1%) participant was missing data in the metformin group and three (1%) were missing data in the placebo group; pre-pregnancy weight was self-reported. ‡Seven (3%) participants were missing data in the metformin group and six (2%) were missing data in the placebo group. §48 (19%) participants were missing data in the metformin group and 45 (18%) were missing data in the placebo group. ¶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. ‖Two (<1%) participants were missing data in the metformin group. **Comprised smoking during pregnancy, alcohol consumption during pregnancy, or recreational drug use during pregnancy. ††One (<1%) participant in the metformin group listed retinopathy but did not indicate type. ‡‡One (<1%) participant in the metformin group developed gestational hypertension before randomisation. §§12 (5%) participants were missing data in the metformin group and ten (4%) were missing data in the placebo group.

Table 1: **Baseline characteristics**

metformin. Women were asked to take the pills for the duration of the pregnancy.

Outcomes

The primary outcome was a composite of fetal and neonatal outcomes including one or more of the following: pregnancy loss (miscarriage, termination, stillbirth, or neonatal death up to 28 days), preterm birth (<37 weeks' gestation), birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycaemia, and NICU admission lasting >24 h; appendix p 34). All components of the primary composite outcome were centrally adjudicated except for preterm birth, which was calculated from the estimated due date.

Secondary maternal outcomes included glycaemic control, hypertensive disorders, caesarean section, gestational weight gain, and insulin dose. Glycaemic control was assessed by HbA_{1c} and capillary glucose measures (appendix p 20).

Key secondary neonatal outcomes included individual outcomes in the composite, birthweight measures (large for gestational age [birthweight >90th percentile], extreme large for gestational age (birthweight >97th percentile), small for gestational age [birthweight <10th percentile]) using Canadian national growth curves adjusted for sex and gestational age,[18] birthweight (≥4000 g), cord blood C-peptide, neonatal adiposity outcomes (fat mass, calculated using the mathematical model proposed by Catalano and colleagues,[19] which includes birthweight, length, and flank skin fold; and skinfold thicknesses), gestational age at birth, and

length of infant hospital stay (appendix p 35). As part of a sensitivity analysis we calculated customised birthweight centiles using Gestational Related Optimal Weight (appendix p 29).[20]

Statistical analysis

Using a population-based Canadian perinatal database,[21] we calculated that we could expect participants to have an absolute risk of 50% for the primary composite outcome. To have 80% power to detect a 25% relative risk (RR) reduction (12·5% absolute reduction), at a two-sided significance level of 5%, we calculated that we would need 492 participants, and accounting for loss to follow-up we aimed for 500 participants.

For baseline covariates, appropriate summary statistics (means, medians, percentages, and measures of dispersion) were generated within treatment group. For the primary composite neonatal outcome, we calculated the relative risk and 95% CI between groups, stratifying by site and BMI using a log-binomial regression model. Any variables with potential imbalances between groups were added in a sensitivity analysis; this criterion led to one such analysis on the timing of the diabetes diagnosis. We also included an additional analysis assessing the variation in the treatment effect with gestational age at first exposure to drug. An intention-to-treat analysis was used, with a plan to use logistic regression in a multiple imputation procedure for the primary outcome if the outcome was missing in more than 5% of infants, which could happen if a woman withdrew or was lost to follow-up or if components of the composite outcome were missing for an infant whose observed components did not satisfy the composite outcome criteria. In this case we also planned to do a complete case analysis in which the data that were available would be used for analysis of the composite outcome without imputation. We also planned that in the best-case scenario all missing values would be replaced with negative results for the composite outcome and in the worst-case scenario all missing values would be replaced with a positive result for the composite outcome.

Continuous secondary outcomes were compared using ANOVA with treatment group and baseline BMI group as categorical variables. For binary outcomes, analyses of the secondary outcomes were also adjusted for BMI group and site if the number of events was greater than 50. For 20–50 events, only BMI group was included and for fewer than 20 events, simple two-group comparisons were used. For secondary binary events a log-binomial regression was used unless outcomes were rare outcomes, in which case we used Fisher's exact test. When possible, a baseline value for the follow-up variable (eg, HbA_{1c}) was added to the model. Two pre-specified subgroup analyses assessed a differential response to treatment according to whether (1) BMI at randomisation was lower than 30 kg/m² or 30 kg/m² or more, and (2) start of treatment was at less than 16 or 16 weeks' or more gestation. A pre-specified per-protocol analysis was done excluding women who discontinued medication, withdrew, or had no medication information. We used R (version 3.6.3) for the analysis. A data safety monitoring board oversaw the trial.

The trial was registered with ClinicalTrials.gov, NCT01353391.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 25, 2011, and Oct 11, 2018, we randomly assigned 502 women to either metformin (n=253 [50%])

	Metformin (n=240)	Placebo (n=242)	p value	Effect size (95% CI)
Composite primary outcome*	94/233 (40%)	95/240 (40%)	0·86	RR 1·02 (0·83 to 1·26)
Pregnancy loss†	13/227 (6%)	14/236 (6%)	0·81	RR 0·96 (0·46 to 2·01)
Spontaneous abortion or miscarriage	4 (2%)	4 (2%)	0·97	RR 0·98 (0·25 to 3·79)
Stillbirth (≥20 weeks gestation)‡	2 (<1%)	7 (3%)	0·11	RR 0·28 (0·06 to 1·32)
Termination	2 (<1%)	2 (<1%)	0·84	RR 0·82 (0·12 to 5·5)
Neonatal death <28 days§	5/227 (2%)	1/236 (<1%)	0·14	RR 4·96 (0·61 to 40·63)
Livebirths	232	229	..	..
Preterm birth <37 weeks	60 (26%)	47 (21%)	0·16	RR 1·27 (0·91 to 1·77)
Birth injury¶	1/231 (<1%)	3/228 (1%)	0·37	RR 0·36 (0·04 to 3·36)
Respiratory distress syndrome¶	11/231 (5%)	8/228 (4%)	0·49	RR 1·36 (0·56 to 3·29)
Neonatal hypoglycaemia¶	27/231 (12%)	34/228 (15%)	0·41	RR 0·82 (0·52 to 1·30)
NICU admission >24 h¶	51/231 (22%)	46/228 (20%)	0·56	RR 1·10 (0·79 to 1·53)
Gestational age at birth, weeks	37·5 (2·2)	37·6 (2·0)	0·33	Difference −0·2 (−0·6 to 0·2)
Birthweight, g	3156 (742)	3375 (742)	0·0016	Difference −0·44 (−0·70 to −0·18)
Birthweight Z score	−0·01 (1·47)	0·45 (1·40)	0·0009	Difference −0·28 (−0·45 to −0·10)
Large for gestational age, >90th centile (adjudicated using Kramer[23])	50 (22%)	66 (29%)	0·067	RR 0·74 (0·54 to 1·02)
Extreme large for gestational age, >97th centile (using Kramer[23])	20 (9%)	34 (15%)	0·041	RR 0·58 (0·34 to 0·97)
Birthweight ≥4000 g	28 (12%)	44 (19%)	0·046	RR 0·65 (0·43 to 0·99)
Small for gestational age, <10th centile (using Kramer[23])‖	30 (13%)	15/228 (7%)	0·026	RR 1·96 (1·10 to 3·64)
Sum of skinfolds, mm**	16·0 (5·0)	17·4 (6·2)	0·024	Difference −1·4 (−2·6 to −0·2)
Neonatal body fat mass††[24]	13·2 (6·2)	14·6 (5·0)	0·017	Difference −1·5 (−2·7 to −0·3)
Cord blood C-peptide (pmol/L)‡‡	673 (435); 569 (360–901)	758 (595); 626 (433–878)	0·10	Ratio of means 0·88 (0·72 to 1·02)
Shoulder dystocia	4 (2%)	4 (2%)	1·0	RR 0·96 (0·25 to 3·69)

(Table 2 continues on next page)

or placebo (n=249 [50%]). 233 (92%) women in the metformin group and 240 (96%) women in the placebo group were available for the primary outcome (figure 1). The last woman gave birth on April 24, 2019, and outcome collection was completed on June 5, 2019.

Overall, baseline characteristics were well balanced (table 1; appendix pp 13, 14). The mean age of participants was 35 years, and 194 (77%) women in the metformin group and 190 (76%) in the placebo group had obesity, and 176 (70%) in the metformin group and 174 (70%) in the placebo group identified as non-European (table 1). 109 (43%) in the metformin group and 108 (43%) in the placebo group were considered socioeconomically disadvantaged, defined as having either immigrated within 5 years of study entry, being single, or having a highest educational attainment of secondary school or less. Although these criteria are not validated measures of socioeconomic disadvantage, each measure by itself has been associated with low socioeconomic status.[22] 64 (13%) of 500 women were immigrants, with 33 (13%) of 251 in the metformin group and 31 (12%) of 249 in the placebo group having immigrated within the past 5 years. 160 (63%) participants in the metformin group and 148 (59%) in the placebo group reported metformin use during the first trimester (table 1).

The median follow-up across livebirths and stillbirths was 20·9 weeks (IQR 17·6–24·1). We found no difference between the intervention groups in the proportion of completed visits (appendix p 15); however, more women in the metformin group than in the placebo group reported that gastrointestinal intolerance was the cause of reducing the pill intake below four pills per day (appendix p 17). Overall pill compliance (defined as total pills taken divided by the total that should have been taken, stopping at delivery or time of withdrawal and excluding patients who had no bottles returned) was 77% in both groups, with approximately 75% of women taking 70% or more of the study pills (appendix p 16). At 6 weeks post partum, 127 (60%) women in the metformin group thought they had been on metformin in the trial, and 77 (35%) in the placebo group thought they were on metformin (appendix p 18).

Because 29 (6%) women were missing primary outcome data, the RR and risk difference of the primary outcome were estimated through multiple imputation (appendix p 12). We found no significant difference in the primary composite outcome between the metformin and placebo groups (table 2). In a sensitivity analysis, we found no significant difference in the primary composite outcome after adjustment for the timing of the diabetes diagnosis (RR 0·98 [95% CI 0·79–1·21). Complete case data, and best-case or worst-case scenarios showed similar results (appendix p 19).

By the end of pregnancy, women in the metformin group achieved better glycaemic control than did those in the placebo group (mean HbA_{1c} at 34 weeks' gestation 41·0 mmol/mol [SD 8·5] *vs* 43·2 mmol/mol [SD –10]; 5·90% [SD 0·78] *vs* 6·10% [0·94]; p=0·015; table 3) and lower mean glucose (6·05 mmol/L [0·93] *vs* 6·27 mmol/L [0·90]; appendix p 20). We found more episodes per week of mild hypoglycaemia in the metformin group than in the placebo group. However, the number of women with mild hypoglycaemic episodes was similar between the groups (appendix p 23). We found no difference in the number of severe hypoglycaemic episodes (appendix p 23).

Metformin-treated women required less insulin (total daily insulin dose by 34 weeks' gestation), and total insulin dose as measured by units per kg per day was lower in the metformin group (table 3) than in the placebo group, as was the percentage of women taking 2 units per kg per day or more (appendix p 24).

Women in the metformin group gained less overall weight and less weight per week than did women in the placebo group (table 3). Fewer women in the metformin group than in the placebo group had excessive gestational weight gain according to the Institute of Medicine (IOM) guidelines (appendix p 25).[25] More women in the metformin group than in the placebo group gained weight below the IOM recommendations (appendix p 25).

Fewer women in the metformin group had caesarean sections than did those in the placebo group. We found no significant difference in hypertensive disorders

	Metformin (n=240)	Placebo (n=242)	p value	Effect size (95% CI)
(Continued from previous page)				
Hyperbilirubinaemia§§	51/227 (23%)	37/227 (16%)	0·06	RR 1·43 (0·99 to 2·07)
Congenital anomaly§§	7/227 (3%)	13/227 (6%)	0·16	RR 0·52 (0·22 to 1·28)
Length of hospital stay until first discharge home, days¶¶	5·6 (7·4)	5·5 (8·1)	0·51	Difference –0·3 (–1·4 to 0·7)

Data are n (%), mean (SD), or median (IQR), unless otherwise indicated. All analyses were intention to treat. Analysis of the primary composite outcome was adjusted for BMI group assessed at time of randomisation and site. Analyses of the secondary outcomes were also adjusted for BMI group and site if outcomes were continuous, or, for binary outcomes, if the number of events was greater than 50. For 20–50 events, only BMI group was included and for <20 events, simple two-group comparisons were used. RR=risk ratio. NICU=neonatal intensive care unit. BMI=body mass index. *Composite primary outcome: pregnancy loss (miscarriage, termination, stillbirth, or neonatal death), preterm birth, birth injury, respiratory distress, neonatal hypoglycaemia, or NICU lasting >24 h. Seven (3%) participants in the metformin group and two (<1%) in the placebo group were missing data. †Early and late pregnancy loss and neonatal death (spontaneous abortion or miscarriage, termination, stillbirth, or neonatal death). The 28-day neonatal death form was missing for 13 (5%) participants in the metformin group and six (3%) in the placebo group. ‡Reasons for stillbirths were two unknown in the metformin group; and one intrauterine fetal death, one ketoacidosis in mother, one twisted umbilical cord, one preterm premature rupture of membranes, one spontaneous rupture of membranes, one severe oligohydramnios, and one cervical insufficiency in the placebo group. §Causes of death were four complications of preterm birth and one severe intrauterine growth restriction + cardiac abnormalities in the metformin group; one complications of preterm birth in the placebo group. ¶One (<1%) missing in the metformin group and one (<1%) missing in the placebo group. ||One (<1%) gestational age at birth in the placebo group was 21 weeks and 3 days, so Kramer could not be used to calculate small for gestational age, but based on weight, the baby was not large for gestational age. **Triceps, subscapular, and supra-iliac skinfolds (n=156 infants in the metformin group and n=179 in the placebo group). ††Included 155 infants in the metformin group and 180 infants in the placebo group. ‡‡143 cord blood serum samples in the metformin group and 142 cord blood serum samples in the placebo group were included in the analysis; estimated effect sizes and p values were calculated in the model using log-values then transformed back to give ratio of means. §§Five (4%) participants in the metformin group and two (1%) in the placebo group were missing data. ¶¶Nine (4%) participants in the metformin group and two (<1%) in the placebo group were missing data.

Table 2: **Neonatal outcomes**

	Metformin (n=240)	Placebo (n=242)	p value	Effect size (95% CI)
Maternal weight gain, kg*				
Overall weight gain	7·2 (5·3)	9·0 (4·7)	<0·0001	Difference −1·8 (−2·7 to −0·9)
Weekly weight gain	0·4 (0·3)	0·5 (0·3)	<0·0001	Difference −0·10 (−0·15 to −0·05)
Last HbA_{1c} concentration in pregnancy, mmol/mol†‡	41·0 (8·5)	43·2 (−10)	0·015	Difference −0·18 (−0·33 to −0·03); difference −2·0 (−3·6 to −0·3)
Last HbA_{1c} concentration in pregnancy, %	5·90% (0·78)	6·10% (0·94)	0·015	Difference −0·18 (−0·33 to −0·03); difference −2·0 (−3·6 to −0·3)
Total insulin dose at 34 or 36 weeks, units per kg per day§	1·1 (1·0)	1·5 (1·1)	<0·0001	Difference −0·4 (−0·5 to −0·2)
Total insulin dose at 34 or 36 weeks, units per day¶	109·8 (105·1)	155·3 (134·0)	<0·0001	Difference −43·9 (−61·5 to −26·2)
Long-acting insulin at 34 or 36 weeks, units per day‖	42·8 (46·0)	55·7 (47·6)	0·004	Difference −12·7 (−21·4 to −4·0)
Short-acting insulin at 34 or 36 weeks, units per day**	66·9 (75·1)	99·1 (108·8)	<0·0001	Difference −32·0 (−49·7 to −14·4)
Caesarean section††	125/234 (53%)	148/236 (63%)	0·031	RR 0·85 (0·73 to 0·99)
Primary caesarean section	65/125 (52%)	68/148 (46%)	0·32	RR 1·13 (0·89 to 1·44)
Any hypertensive disorder‡‡	55 (23%)	56 (23%)	0·93	RR 0·99 (0·72 to 1·35)
Gestational hypertension	13 (5%)	15 (6%)	0·82	RR 0·92 (0·46 to 1·85)
Worsening chronic hypertension during pregnancy§§	20/237 (8%)	22 (9%)	0·68	RR 0·89 (0·51 to 1·56)
Pre-eclampsia	37 (15%)	30 (12%)	0·29	RR 1·27 (0·82 to 1·97)

Data are mean (SD), n/N (%), or n (%), unless otherwise specified. All analyses were intention to treat. Analyses of the secondary outcomes were adjusted for BMI group assessed at time of randomisation and site if outcomes were continuous, or, for binary outcomes, if the number of events was greater than 50. For 20–50 events, only BMI group was included and for fewer than 20 events, simple two-group comparisons were used. BMI=body mass index. RR=risk ratio. *Nine (4%) participants in the metformin group and four (2%) in the placebo group were missing data. Overall and weekly weight gain was calculated from measured weight at randomisation. †227 (95%) of 240 participants in the metformin group and 235 (97%) of 242 in the placebo group. ‡After adjusting for baseline HbA_{1c} at randomisation. §208 (98%) of 212 participants in the metformin group and 211 (99%) of 213 in the placebo group. ¶211 (99%) of 212 participants in the metformin group and 211 (99%) of 213 in the placebo group. ‖212 (100%) of 212 participants in the metformin group and 213 (100%) of 213 in the placebo group. **211 (99%) of 212 participants in the metformin group and 211 (99%) of 213 in the placebo group. ††234 (99%) of 236 participants based on available method of birth data. ‡‡Gestational hypertension, worsening chronic hypertension, or pre-eclampsia. §§Three (1%) participants were missing data in the metformin group.

Table 3: **Maternal outcomes**

(table 3), diabetes complications (appendix p 26), or maternal length of hospital stay (appendix p 27).

Birthweight was lower in the metformin group than in the placebo group, with reduced extreme large for gestational age and birthweight 4000 g or more (table 2). We also found reductions in neonatal adiposity measures in the metformin group (skinfold thicknesses, abdominal circumference, and neonatal fat mass; table 2; appendix p 28).

We found no difference in the components of the composite outcome between groups. We found no difference in gestational age at birth, shoulder dystocia, or hyperbilirubinaemia (table 2). Neonatal length of hospital stay was similar between the groups (table 2).

The distribution of birthweights was shifted downwards across the entire birthweight spectrum in those on metformin (figure 2). More infants in the metformin group were small for gestational age (13% *vs* 7%; RR 1·96 [95% CI 1·10–3·64]; p=0·03) using Canadian population charts[18] (table 2) and customised centiles (appendix p 29).[20]

Intolerance to the study drug was not different between the groups when reporting adverse events (table 4). Fewer women reported serious adverse events in the metformin group than in the placebo group, but the total number of serious maternal adverse events was not significantly different between the groups (table 4). When examining total maternal adverse events, we found a similar number of events and a similar number of women reporting events in both groups (table 4). We found a similar number of infant adverse and serious adverse events reported in both groups (table 4).

In a pre-specified subgroup analysis of the primary outcome stratified by maternal BMI, we found no significant variation in the treatment effect between groups (ratio of RRs 1·0, 0·58–1·72; appendix p 32). In the subgroup analysis stratified by earlier (<16 weeks) and later randomisation, we found no between-group difference (appendix p 32). The effect of metformin did not appear to differ according to the gestational age at which a woman entered the study (appendix p 36).

The per-protocol analysis results were concordant with the primary analysis for the primary outcome (appendix p 30).

Discussion

We found no difference between women who received metformin and those receiving placebo in a composite of neonatal morbidity and mortality. However, metformin-treated women had better glycaemic control, lower insulin requirements, less gestational weight gain, and fewer caesarean births than women in the placebo group did. Infants of mothers taking metformin weighed less, were less likely to be extremely large for gestational age, and less likely to weigh 4000 g or more at birth compared with infants born to mothers taking placebo. Additionally, metformin-exposed infants displayed reduced adiposity with reduced skinfold thicknesses, abdominal circumference, and fat mass. In keeping with lower adiposity and infant size, we observed a higher proportion of babies who were small for gestational age in the metformin group than in the placebo group.

Notably, by contrast with some previous studies,[11,12] we did not find a difference in serious neonatal outcomes when metformin was added to insulin. Given the far greater statistical power and rigour of the MiTy trial compared with previous trials, this discrepancy is most likely explained by previous studies having small sample sizes, no masking, and excluding women already on insulin.[12] The many benefits observed in the metformin

group in our study, including improved glycaemic control and lower rates of very large infants, did not translate into improvements in the composite outcome. In a previously published randomised trial of women with type 1 diabetes,[26] we observed that improved glycaemic control that was achieved through continuous glucose monitoring led to a significant reduction in large-for-gestational-age infants and serious neonatal outcomes such as neonatal hypoglycaemia and NICU admissions.[26] The absence of similar congruence between indices of infant size and serious neonatal adverse outcomes in the MiTy trial might relate to the lower overall rate of large-for-gestational-age infants and hyperglycaemia in women with type 2 diabetes. We did not find a difference in stillbirth and perinatal mortality, but the study did not have power to detect differences in these rare outcomes, so conclusions should thus be drawn with caution.

We found improved glycaemic control and lower insulin requirements in the metformin group, with fewer women requiring higher insulin doses than in the placebo group. This finding is in agreement with a study[23] of 390 patients with insulin-treated type 2 diabetes outside of pregnancy, in which metformin use was associated with improved glycaemic control and a reduced insulin dose of 7·5 units per day. In MiTy, women on metformin had a substantially greater reduction of 45 units fewer insulin per day. Given that almost half of participants were considered to have low socioeconomic status, such a reduction in insulin dose could result in substantial cost savings improving affordability for lower-income women with type 2 diabetes.

Women on metformin also gained less weight during pregnancy than did those who received placebo, consistent with findings in previous trials in women with gestational diabetes.[8] This finding might be due to the reduced insulin requirements, or to direct effects of metformin, which can cause anorexia and weight reduction via increases in growth differentiation factor 15 concentrations.[24] Excess gestational weight gain is associated with an increase in the risk of pre-eclampsia, large-for-gestational-age infants, and preterm birth, especially in women with obesity,[3] and increases the risk of postpartum weight retention. In our study, in which 76% of women had obesity before pregnancy, this finding represents an additional accrual of adipose tissue, further increasing the risk of long-term obesity.

We found that infants of women in the metformin group had a lower birthweight, were less likely to be extremely large, and had reduced adiposity compared with those born in the placebo group, which is consistent with findings of previous studies in women with gestational diabetes.[9] Several mechanisms might explain these findings. In our study, women who received metformin had better glycaemic control and less excess maternal weight gain, both of which can lower the risk of being born large for gestational age. Also, women on metformin required less insulin than did those in the placebo group,

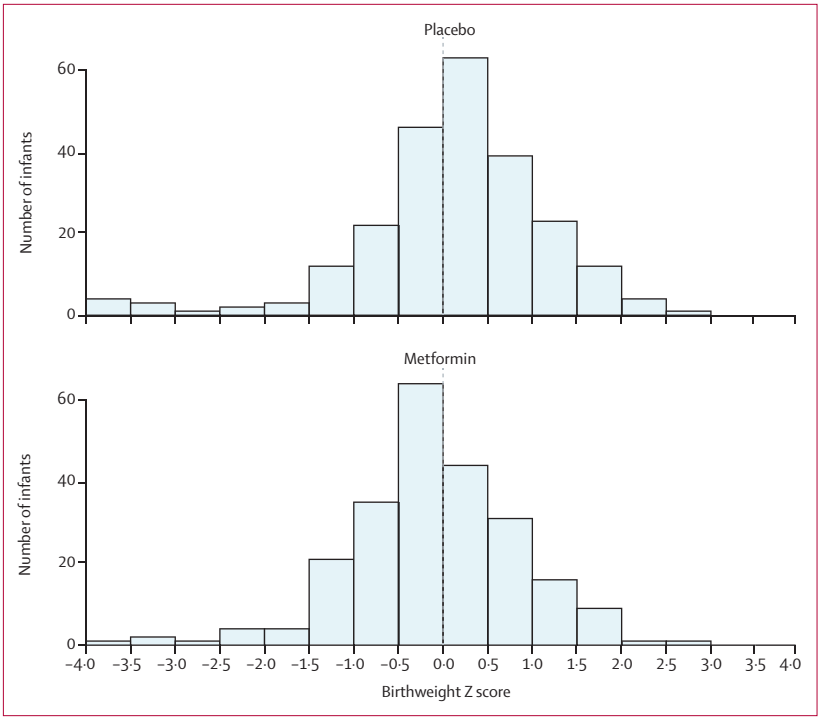

Figure 2: **Birthweight distributions in infants of women in the metformin and placebo groups**

which can influence maternal weight gain and thus infant size.[3] Another possible mechanism might be a direct effect of metformin on fetal growth.[6] Metformin activates AMP kinase and leads to the inhibition of the mechanistic target of the rapamycin (mTOR) pathways, which are regulators of placental amino acid transport.[6] The inhibition of these and other growth differentiation pathways could contribute to the attenuated fetal growth observed.

In addition to fewer large infants, we found more infants who were small for gestational age in the metformin group than in the placebo group. This finding was reported in one previous study of women with type 2 diabetes[12] and is important because infants who are small for gestational age might have an increased risk of perinatal complications[27] and potential long-term consequences such as neurodevelopmental delay affecting school performance,[28] obesity, hypertension, diabetes, and cardiovascular disease, similar to infants of mothers with under-nutrition.[29] The distribution of birthweight was shifted downwards across the entire population of metformin-exposed infants relative to the placebo group. Whether this increase in the number of small infants represents smaller but healthy infants or pathologically growth-restricted infants is unclear. The underlying cause of being born small for gestational age in the metformin-exposed infants is unknown. The increased number of small infants could be related to effects of metformin on mothers leading to reduced food intake.[30] This change could affect weight gain, glycaemic control, and nutrient supply. Inhibition of mTOR might

	Metformin (n=253)	Placebo (n=249)	Effect size (95% CI)
Women reporting adverse events	76 (30%)	87 (35%)	Rate ratio 0·86 (0·67–1·11)
Total maternal adverse events	139	170	Rate ratio 0·83 (0·62–1·11)
Gastrointestinal	38 (27%)	38 (22%)	..
Nausea or vomiting	15 (11%)	19 (11%)	..
Allergies	2 (1%)	1 (<1%)	..
Cardiac	3 (2%)	5 (3%)	..
Dermatological	2 (1%)	4 (2%)	..
Gynaecological	1 (<1%)	2 (1%)	..
Haematological	3 (2%)	5 (3%)	..
Headaches	6 (4%)	11 (7%)	..
Hyperglycaemia	0	2 (1%)	..
Infections	6 (4%)	7 (4%)	..
Musculoskeletal	7 (5%)	9 (5%)	..
Neurological	2 (1%)	4 (2%)	..
Obstetric	10 (7%)	6 (4%)	..
Other	0	2 (1%)	..
Otolaryngological	3 (2%)	3 (2%)	..
Ophthalmological	1 (<1%)	0	..
Pneumonia or lower respiratory infection	2 (1%)	1 (<1%)	..
Psychological	3 (2%)	0	..
Renal	0	1 (<1%)	..
Respiratory	28 (20%)	42	..
Thyroid cancer	1 (<1%)	0	..
Urinary tract infection	6 (4%)	8 (5%)	..
Women reporting serious adverse events	5 (2%)	15 (6%)	RR 0·33 (0·11–0·83)
Total maternal serious adverse events	6	16	Rate ratio 0·41 (0·16–1·09)
Respiratory	0	1 (6%)	..
Diabetic ketoacidosis	0	1 (6%)	..
Other	1 (17%)	0	..
Obstetric	1 (17%)	3 (19%)	..
Hyperglycaemia	1 (17%)	2 (13%)	..
Gastrointestinal	0	1 (6%)	..
Cardiac	1 (17%)	3 (19%)	..
Infections	0	1 (6%)	..
Musculoskeletal	0	1 (6%)	..
Renal	1 (17%)	1 (6%)	..
Nausea or vomiting	0	1 (6%)	..
Vascular	1 (17%)	0	..
Psychological	0	1 (6%)	..
Infants with adverse events	1 (<1%)	1 (<1%)	..
Total infant adverse events	1	1	..
Infants with serious adverse events	2 (<1%)	1 (<1%)	..
Total infant serious adverse events	2	1	..
Respiratory	1 (50%)	1 (100%)	..
Weight loss	1 (50%)	0	..

Data are n or n (%), unless otherwise indicated. RR=risk ratio.

Table 4: **Adverse events**

downregulate pathways involved with protein synthesis, cell growth, and proliferation.[6] Metformin inhibits folate-related pathways, which could result in reduced cell growth and nutrient restriction.[6] Metformin might also directly affect placental function and nutrient transfer and might have direct fetal effects affecting the fetal metabolic milieu, cell metabolism, and insulin secretion.[6] In our study, more women in the metformin group gained weight under that of the recommended guidelines, which might have played a role in the increased rate of infants who were small for gestational age. As well, very tight glycaemic control (ie, lower mean glucose of 4·8 mmol/L [86 mg/dL]) has resulted in small-for-gestational-age infants in some studies.[31] However, in our study, glycaemic control in the metformin group was not exceptionally tight (mean glucose 6·1 mmol/L [109 mg/dL]). In studies of non-diabetic women with obesity[32] and women with polycystic ovary syndrome[33] using metformin during pregnancy, no effect on birthweight and no increase in the number of infants born small for gestational age was found, suggesting a direct effect of metformin on growth might be less likely than an indirect effect. Regardless of the cause, understanding the relative implications of these findings is important to properly advise patients who are contemplating the use of metformin during pregnancy.

Such effects on growth might have long-term consequences. In a systematic review and meta-analysis of neonatal, infant, and childhood growth following metformin exposure, results showed that, when compared with infants born to women using insulin with gestational diabetes, neonates born to mothers using metformin exhibited lower birthweights, had a lower ponderal index, and were less likely to be large for gestational age at birth.[9,34] In infancy, the metformin-exposed children were heavier, and by age 5–9 years they had an increased BMI compared with infants whose mothers were given insulin.[9] This finding, however, is based on a paucity of data and divergent findings exist. For example, in one study the authors suggested that the glycaemic milieu during pregnancy is crucial, with protective effects of metformin in infants exposed to poorer glycaemic control but deleterious effects in infants whose mothers had tight glycaemic control during pregnancy.[34] Further research is needed to understand the long-term effects of metformin on children.

In addition to the randomised, double-masked, placebo-controlled design, and low attrition, this trial had several strengths. To our knowledge, this is the first large, appropriately powered, and methodologically sound randomised trial of metformin versus placebo added to insulin in women with type 2 diabetes in pregnancy. The trial had adequate statistical power to detect important effects on the primary outcome and provided a precise estimate of the treatment effect. The participants were from diverse ethnic and socioeconomic backgrounds, making the results generalisable to pregnant women with type 2 diabetes. Pill compliance was good and data collection was almost complete, with almost all randomly assigned women and their neonates included in the primary outcome analysis. The protocol had been previously published and statistical analyses pre-specified. However, some limitations existed.

The trial took 9 years to complete and care practices could have changed over the years. Given that this placebo-controlled, randomised trial was randomly blocked, changes in care are unlikely to have affected the outcome of the trial. The results might not apply to women on metformin alone. However, a trial by Ainuddin and colleagues[12] showed that most women with type 2 diabetes needed insulin in addition to metformin, with only 15% on metformin alone. Although the results do not directly apply to women with gestational diabetes, those with gestational diabetes and marked hyperglycaemia who are diagnosed early in pregnancy might more closely resemble our study population, and thus be affected by these findings. Finally, clearance of metformin is increased in pregnancy and a more marked effect on outcomes might have been seen with a higher dose of metformin.

In summary, although we found no significant difference in the primary composite outcome of serious neonatal outcomes in women with type 2 diabetes treated with metformin or placebo, added to insulin, we found several (secondary, pre-specified) maternal glycaemic and neonatal adiposity benefits in the metformin group, including improved glycaemic control, lower insulin requirements, less weight gain, fewer caesarean births, lower birthweight and adiposity measures, and fewer extreme large-for-gestational-age, but more small-for-gestational-age infants. Understanding the implications of these effects on infants will be important to properly advise patients who are contemplating the use of metformin during pregnancy. Follow-up of metformin-exposed infants into childhood, adolescence, and adulthood will be crucial to gain a broader understanding of the effect of metformin on the future health of exposed infants.

Contributors

DSF, BZ, JJS, EA, EAR, GF, ABA, JFRB, GT, and KEM designed the study. DSF, LED, BZ, JJS, EA, EAR, IGF, EH, ABA, LLL, DS, JFRB, PJK, SYT, GT, and KEM designed the statistical analysis plan. EA, JFRB, PK, JJS, and ST supervised the trial operations, data collections, data quality control, and programming for the statistical analyses. DSF, LED, EAR, ABA, DS, HDM, JJS, and ST contributed to the data collection. DSF, BZ, EA, EAR, GF, ABA, LLL, DS, JFRB, PJK, GT, and KEM provided overall trial oversight. GT and SYT did the statistical analyses. All authors contributed to interpretation of the data. DSF wrote the first draft. All authors reviewed and provided critical revisions to the manuscript.

Declaration of interests

DSF reports grants from the Canadian Institutes of Health Research, Lunenfeld-Tanenbaum Research Institute, and the University of Toronto Department of Medicine; non-financial support from Apotex, Bayer (Asencia), and Roche Diabetes Care; and personal fees from Medtronic and Novo Nordisk. IGF reports grants from the Canadian Institutes of Health Research. PJK reports grants from the Canadian Institutes of Health Research. JJS reports grants from the Canadian Institutes of Health Research. ST reports grants from the Canadian Institutes of Health Research. All other authors declare no competing interests.

Data sharing

The data are available from the corresponding author, upon providing a detailed protocol for the proposed study, information about the funding and resources you have to carry out the study, and approval by the MiTy Steering Committee.

Acknowledgments

The trial was funded by the Canadian Institutes of Health Research, the Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada, and the Department of Medicine, University of Toronto, Toronto, ON, Canada. The study drugs, metformin and placebo, were provided by Apotex, Toronto, ON, Canada, and Bayer (Asencia) and Roche Diabetes Care provided the glucometers and strips. We thank all the women with type 2 diabetes who participated in the trial. We also acknowledge the invaluable support from the 29 diabetes research and clinical care teams and the Clinical Trials Services research team at Sunnybrook Research Institute, Toronto, ON, Canada. We thank the data safety monitoring board for overseeing the trial: Kevin Thorpe, Lelia Duley, and Michael Bracken. We would also like to acknowledge our steering committee member Arne Ohlsson for his very wise counsel and dedication to the trial. Arne Ohlsson unfortunately passed away before the writing of this manuscript. We are indebted to him for his important contributions and support for this trial.

References

1 Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. *Diabetes Care* 2014; **37:** 1590–96.

2 Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol* 2018; **6:** 69–80.

3 Santos S, Voerman E, Amiano P, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. *BJOG* 2019; **126:** 984–95.

4 Murphy HR, Bell R, Cartwright C, et al. Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. *Diabetologia* 2017; **60:** 1668–77.

5 Langer O, Anyaegbunam A, Brustman L, Guidetti D, Levy J, Mazze R. Pregestational diabetes: insulin requirements throughout pregnancy. *Am J Obstet Gynecol* 1988; **159:** 616–21.

6 Nguyen L, Chan SY, Teo AKK. Metformin from mother to unborn child—are there unwarranted effects? *EBioMedicine* 2018; **35:** 394–404.

7 Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril* 2005; **83:** 1575–78.

8 Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. *Diabet Med* 2017; **34:** 27–36.

9 Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: a systematic review and meta-analysis. *PLoS Med* 2019; **16:** e1002848.

10 Cesta CE, Cohen JM, Pazzagli L, et al. Antidiabetic medication use during pregnancy: an international utilization study. *BMJ Open Diabetes Res Care* 2019; **7:** e000759.

11 Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. *Arch Gynecol Obstet* 2014; **289:** 959–65.

12 Ainuddin JA, Karim N, Zaheer S, Ali SS, Hasan AA. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. *J Diabetes Res* 2015; **2015:** 325851.

13 Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle Bu Teaching Hospital: a randomized clinical trial. *PLoS One* 2015; **10:** e0125712.

14 Hickman MA, McBride R, Boggess KA, Strauss R. Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial. *Am J Perinatol* 2013; **30:** 483–90.

15 Waheed S, Malik FP, Mazhar SB. Efficacy of metformin versus insulin in the management of pregnancy with diabetes. *J Coll Physicians Surg Pak* 2013; **23:** 866–69.

16 Feig DS, Berger H, Donovan L, et al. Diabetes and pregnancy. *Can J Diabetes* 2018; **42** (suppl 1): S255–82.

17 Feig DS, Murphy K, Asztalos E, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. *BMC Pregnancy Childbirth* 2016; **16:** 173.

18 Kramer MS, Platt RW, Wen SW, et al. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* 2001; **108:** E35.

19 Catalano PM, Thomas AJ, Avallone DA, Amini SB. Anthropometric estimation of neonatal body composition. *Am J Obstet Gynecol* 1995; **173:** 1176–81.

20 Gardosi J, Francis A, Turner S, Williams M. Customized growth charts: rationale, validation and clinical benefits. *Am J Obstet Gynecol* 2018; **218** (2S): S609–18.

21 Joseph KS, Fahey J, Canadian Perinatal Surveillance System. Validation of perinatal data in the Discharge Abstract Database of the Canadian Institute for Health Information. *Chronic Dis Can* 2009; **29:** 96–100.

22 Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc* 2007; **99:** 1013–23.

23 Wulffele MG, Kooy A, Lehert P, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care* 2002; **25:** 2133–40.

24 Coll AP, Chen M, Taskar P, et al. GDF15 mediates the effects of metformin on body weight and energy balance. *Nature* 2020; **578:** 444–48.

25 Rasmussen KM, Yaktine AL, US Institute of Medicine. Committee to reexamine IOM pregnancy weight guidelines. Weight gain during pregnancy: reexamining the guidelines. Washington DC, USA: National Academies Press, 2009.

26 Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017; **390:** 2347–59.

27 Mendez-Figueroa H, Truong VT, Pedroza C, Chauhan SP. Morbidity and mortality in small-for-gestational-age infants: a secondary analysis of nine MFMU network studies. *Am J Perinatol* 2017; **34:** 323–32.

28 Savchev S, Sanz-Cortes M, Cruz-Martinez R, et al. Neurodevelopmental outcome of full-term small-for-gestational-age infants with normal placental function. *Ultrasound Obstet Gynecol* 2013; **42:** 201–06.

29 Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993; **36:** 62–67.

30 Coll AP, Chen M, Taskar P, et al. GDF15 mediates the effects of metformin on body weight and energy balance. *Nature* 2020; **578:** 444–48.

31 Langer O, Levy J, Brustman L, Anyaegbunam A, Merkatz R, Divon M. Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 1989; **161:** 646–53.

32 Chiswick C, Reynolds RM, Denison F, et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2015; **3:** 778–86.

33 Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010; **95:** e448–55.

34 Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. *BMJ Open Diabetes Res Care* 2018; **6:** e000456.