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The Effect of Metformin on Insulin Requirement, Glycaemic Control and Weight Gain in Type 1 Diabetes During Pregnancy—a Randomised, Placebo-Controlled Multicentre Study

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ABSTRACT

Aim: Our aim was to ascertain whether metformin can reduce insulin requirement without compromising glycaemic control during pregnancy in women with type 1 diabetes.

Methods: A total of 126 pregnant women with type 1 diabetes were recruited for a randomised, double-blind, placebo-controlled multicentre study. The primary outcome was total insulin change, defined as the difference between baseline and third trimester maximum insulin dose (IU).

Results: Fifty women in the placebo group and 51 women in the metformin group completed the study. A predetermined sample size of 200 participants was not achieved. There was no significant difference in the primary outcome, that is, in the change of total insulin requirement (33 vs. 27 IU, $p = 0.193$). However, the metformin group showed a significantly lower increase in the prandial insulin change, with 24 versus 14 IU ($p = 0.014$) and 0.3 versus 0.2 IU/kg ($p = 0.048$). In the exploratory subgroup analysis, metformin attenuated prandial insulin increase in women with high BMI (> 25 kg/m^2) or high baseline insulin requirement

(> 40 IU) (25 vs. 15 IU, $p = 0.028$, 30 vs. 14 IU, $p = 0.007$). Weight gain remained more often within target in the metformin group (20% vs. 40%, $p = 0.029$). A similar weight benefit was observed in subgroups (BMI> 25 kg/m^2 8% vs. 32%, $p = 0.005$, insulin requirement> 40 IU 6% vs. 34%, $p = 0.004$). No differences were seen in glycaemic control or neonatal outcome between the groups.
Conclusions: Metformin was not shown to affect total insulin change but reduced the prandial insulin change and improved weight gain control especially in insulin-resistant subgroups. These findings warrant further studies on metformin as an adjunctive medicine.
Trial Registration: ClinicalTrials.gov: NCT03765359.

1 | Introduction

The key element in the management of pregnancy among women with type 1 diabetes is maintaining optimal glycaemic control through active insulin therapy. Physiological insulin resistance (IR) during pregnancy is caused by hormones, cytokines and adiponectins produced by the placenta and maternal adipose tissue [1]. IR in healthy pregnancies is necessary to ensure foetal glucose supply and growth. Hyperinsulinemia, dyslipidemia, hyperglycaemia and obesity may cause mild inflammation that exacerbates IR [1–3]. Furthermore, excess weight gain during pregnancy affects insulin requirements in women with type 1 diabetes [4–7]. In women with diabetes, IR is even higher or its management is more challenging due to insulin therapy.

Metformin is mainly used to treat hyperglycaemia and IR in type 2 diabetes. It improves glycaemic control and IR mainly by reducing glucose production in the liver and increasing utilisation of glucose in the skeletal muscles [8]. In two recent placebo-controlled trials, the addition of metformin to insulin in pregnant women with type 2 diabetes improved glycaemic control, lowered the insulin requirement and decreased weight gain [9] or caused no significant changes in maternal therapeutic aspects [10]. In both metformin studies on women with type 2 diabetes, the rate of large-for-gestational-age newborns was reduced [9, 10].

A recent meta-analysis showed that metformin can be used effectively and safely in gestational diabetes (GDM). In GDM, metformin was associated with lower maternal weight gain and lower risk for neonatal macrosomia compared with insulin treatment. Metformin did not affect the rate of preterm deliveries even if it decreased gestational age at delivery compared with insulin treatment. Furthermore, neonatal hypoglycaemia and admissions to the neonatal intensive care unit decreased with metformin treatment [11].

Our aim was to study whether metformin as an add-on therapy to insulin in women with type 1 diabetes reduces insulin requirement and weight gain during pregnancy compared with a placebo, without compromising glycaemic control. In pregnancies complicated by type 1 diabetes, it is essential to maintain glycaemic control as close to physiological levels as possible by the active administration of insulin.

2 | Materials and Methods

2.1 | Study Design

This was a randomised, double-blind, placebo-controlled multicentre study conducted at four university hospitals (Helsinki, Oulu, Tampere, and Turku) and in the former Central Finland Health Care District. These centres together take care of approximately 50% of deliveries in Finland annually (Supporting Information) Table S1).

2.2 | Participants

The inclusion criterion was singleton pregnancy in women with type 1 diabetes in the first trimester of pregnancy. The exclusion criteria were multiple pregnancy, coronary disease, kidney transplant, chronic liver disease, inflammatory bowel disease, systemic lupus erythematosus, asthma or rheumatoid arthritis with repeated corticosteroid therapy, nephropathy (urinary albumin excretion = UEA ˃200 μg/min, urinary albumin-to-creatinine ratio = UACR ˃30 mg/mmol or eGFR˂60 mL/min/1,73 m^2), proliferative retinopathy (under treatment or untreated), gastroparesis, smoking, substance use disorder, BMI < 18 kg/m^2, or severe nausea or vomiting in pregnancy.

Both insulin delivery methods, multiple daily injections and insulin pumps, were accepted in the study.

2.3 | Study Preparation

The study tablets were prepared and packaged by Takeda Pharmaceuticals. Thereafter, the packages were numbered, randomised in the ratio 1:1 in block sizes of six by the pharmaceutical manufacturer (Galena Pharma, Finland) and despatched to the study sites. On randomisation, participants were assigned the packages in numerical order. Galena Pharma provided the randomisation keys in sealed opaque envelopes, which the researcher at the study site stored in a locked cabinet. The sponsor, Tampere University Hospital, had copies of all randomisation keys.

Women with type 1 diabetes fulfiling the inclusion criteria received oral and written information about the study at their first appointment in the maternity outpatient clinics. The participants were recruited as informed consent was obtained during the first trimester by a researcher or by a designated clinician to whom the study was delegated. Randomisation was performed at 11^{+0}–13^{+6} gestational weeks by a researcher, a designated clinician or a study nurse. This visit will be referred to as the baseline visit. The study medication dose was one tablet (placebo or 500 mg metformin) daily and the dosage was increased by one tablet weekly until the target dosage 2 + 2 tablets (placebo or 2 g metformin) was reached.

If a participant could not tolerate the study medicine, the dosage was adjusted to the highest dose tolerated and this was to be increased at a slower pace. A participant could continue in the study if the dose of the study medicine was at least two tablets per day by pregnancy week 20 (Supporting Information S1: Figure S1).

The study period was from 5 August 2019 to 30 June 2022. Enrolment was closed on 31 December 2021 because the slow recruitment caused the study medicine and funding to expire.

2.4 | Outcomes

The primary outcome was total insulin change (IU) defined as the change between the baseline total insulin dose and the maximum total insulin dose during the third trimester of pregnancy.

Secondary outcomes were change in total insulin (IU/kg), prandial insulin (IU and IU/kg) and basal insulin doses (IU and IU/kg) defined as the change between the baseline insulin dose and the maximum insulin dose during the third trimester of pregnancy, weight gain during pregnancy defined as the maximum third trimester value and glycaemic control defined by HbA1c, glucose management indicator (GMI), mean sensor-derived glucose, mean glucose standard deviation (SD), coefficient variation (CV) and time in/below/above pregnancy-specific range (TIRp/TBRp/TARp) each specified as the mean third trimester value. As secondary outcomes, we also evaluated the change in the variables between the baseline value and the specific third trimester value. Maximum insulin doses in the third trimester of pregnancy were also evaluated. The changes in insulin requirement in time were modelled with linear mixed model.

Additionally, the percentage of women whose weight gain was within the recommended limits during pregnancy was calculated. Participants were classified at the baseline visit according to the Copenhagen Guidelines for BMI-adjusted optimal weight gain targets for pregnancies in women with type 1 diabetes: BMI $\leq$ 25 kg/m^2 10–15 kg, 25 < BMI $\leq$ 30 kg/m^2 5–8 kg and BMI > 30 kg/m^2 0–5 kg [11, 12].

Pregnancy outcomes were rate of miscarriages < 22^{+0} weeks of gestation, hypertensive disorders of pregnancy (gestational hypertension or pre-eclampsia) and mode of delivery (vaginal delivery or caesarean section).

Neonatal outcomes were gestational age at delivery, rate of preterm and very preterm deliveries (< 37^{+0} and < 32^{+0} weeks of gestation), birth weight, proportions of large for gestational age (LGA = a newborn weight above the 90th percentile and extremely LGA = a newborn weight above the 97th percentile) and small for gestational age (SGA = a newborn weight below the 10th percentile) neonates, stillbirth (foetal loss $\geq$ 22^{+0} gestational weeks) and neonatal condition (arterial pH, Apgar scores at one minute and five minutes of age, admissions to the neonatal intensive care unit, neonatal hypoglycaemia, and respiratory distress syndrome).

2.5 | Subgroups

As an exploratory analysis, changes in insulin requirement and weight gain were assessed in subgroups to ascertain whether the effect of metformin was more profound among women at greater overall risk of insulin resistance. We used specific cutoffs to categorise participants: BMI greater than 25 kg/m^2 was used to define overweight, and a total baseline insulin requirement exceeding 40 IU/day was used to identify individuals with a high baseline insulin requirement, both measured at baseline.

2.6 | Follow-Up of Pregnancy

The women had appointments at their respective maternity outpatient clinics approximately monthly up to 31^{+6} weeks of gestation, every two weeks between 32^{+0} to 35^{+6} and weekly from 36^{+0} weeks of gestation until delivery. The baseline clinical characteristics (age, previous pregnancies, height, weight, BMI, complications of diabetes, duration of diabetes) were collected at enrolment and the study data (insulin doses, variables associated with glucose balance, weight) were collected prospectively at the study visits (Supporting Information S1: Figure S1).

2.7 | Follow-Up of Glycaemic Control and Diabetes Management

All participants had a glucose sensor according to their clinical needs, that is, intermittently scanned continuous glucose monitoring (isCGM) or real-time continuous glucose monitoring (rtCGM). Glucose sensor data from the previous two weeks were collected at the clinic visits. GMI, TIRp/TBRp/TARp, mean sensor-derived glucose and SD and CV were collected from the isCGM and rtCGM data. Sensor wear time was not noted. Patients with isCGM were advised to scan the sensor at least 10 times daily with a maximum scanning interval of eight hours. The CV was calculated similarly in isCGM and rtCGM as %SD divided by the mean sensor glucose.

At all clinic visits, mean total, basal and prandial insulin dosages from the preceding two-week period were collected. All basal and prandial insulin types were accepted. Women with multiple daily insulin injections were asked to document their insulin dosages. For those using an insulin pump, data were extracted directly from the pump report. Between visits, the participants adjusted their insulin treatment in their everyday lives. Target values for glucose were as follows: fasting 3.9–5.3 mmol/L and postprandial 1 h < 7.8 mmol/L and TIRp 3.5–7.8 mmol/L > 70% [13].

2.8 | Ethics

The study was approved by the national ethics committee TUKIJA (94/06.00.01/2017) and institutional review boards at every study site and registered at EudraCT (2016-005031-32) and ClinicalTrials.gov (**NCT03765359**). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided signed written informed

consent forms. The clinical study protocol was adhered to, and the study was monitored by the monitoring plan (Supporting Information S1: Figure S2). The sponsor of the study was Tampere University Hospital. Takeda Pharmaceuticals provided the study medicines. The company was not involved in the design of the study, the collection, analysis and interpretation of data, writing the report and did not impose any restrictions regarding the publication of the report. Information on serious adverse events and suspected unexpected serious adverse reactions was forwarded to Takeda Pharmaceuticals.

2.9 | Statistics

To have 80% power to detect a clinically significant 15% reduction in total insulin change between the two groups, at a two-sided significance level of 5%, the target sample size was calculated to be 200 participants to support adequate power.

Statistical analysis was performed using SPSS for Windows (version 28.0.1.1 (15)). Data were compared between the two groups. Continuous variables were expressed as means with standard deviations or medians with minimum and maximum values depending on the skewness of the distribution, which was investigated using Shapiro-Wilk test. Percentages were used for categorical variables. Differences between the groups were tested with independent samples *t*-test, Mann-Whitney *U*-test, chi-square test and Fisher's exact test. A p-value < 0.05 was considered statistically significant. No multiplicity correction was applied. Effect size was measured in normally distributed variables with mean difference. Hodges-Lehman estimate was used to compare median difference and Odds Ratio with binary outcomes were compared. In the exploratory analyses no formal interaction tests for effect modification were performed.

Linear regression analysis was performed using baseline insulin requirement, type of insulin delivery (insulin pump or multiple daily injections) and study group as covariates.

Linear mixed models were formed to compare the outcomes known to be associated with duration of pregnancy between the two groups using data from all available weeks of gestation. Models were formed to control for the varying durations of the pregnancies, slight variation in gestational weeks at the study visits and missing measurements. Random intercept was used. Model selection was based on Akaike's information criteria and Schwarz's Bayesian Criterion and the models were compared using 1–3. Degree polynomials of pregnancy weeks.

2.10 | Handling of Missing Data

In the statistical analysis, missing data were not imputed. Missing data are given in tables and figures, some of these as Supporting Information materials. However, linear mixed model analysis is quite robust in handling occasional missing measurements during follow-up.

3 | Results

3.1 | At Baseline

A total of 126 women were recruited and 101 women were randomised. Fifty women in the placebo group and 51 women in the metformin group completed the study (Figure 1). A predetermined sample size of 200 participants was not achieved.

There were no significant differences between the two groups in baseline characteristics (Table 1) except that in the placebo

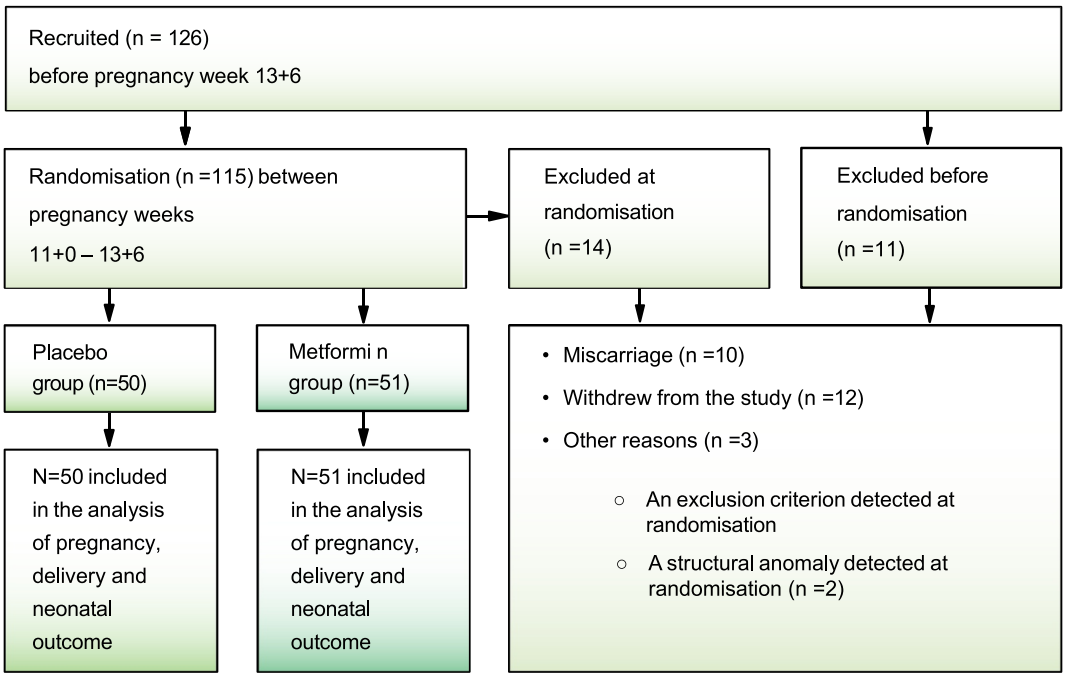

FIGURE 1 | Trial profile. Between August 5, 2019 and December 31, 2021, a total of 126 patients were recruited. Finally, 101 patients completed the study: $n = 50$ in placebo and $n = 51$ in metformin group.

TABLE 1 | Demographic characteristics and baseline visit data.

Demographic data	Placebo group (n = 50) Mean	±SD	Metformin group (n = 51) Mean	±SD	p-value
Age, years	29	±4.8	30	±3.5	0.289
BMI, kg/m^2	27[a]	±4.1	27	±4.8	0.401
Duration of diabetes, years	16	±7.3	19	±7.2	0.011
	n	%	n	%	p-value
Primiparous	14	28	20	39	0.643
Multiple daily insulin injections	29	58	35	69	0.268
Insulin pump	21	42	16	31	0.268
HCL pump	0	0	2	4	0.180
isCGM	39	78	40	78	0.958
rtCGM	11	22	11	22	
Hypertension	5	10	3	6	0.487
Complications of diabetes					
None	20	40	18	35	0.625
Retinopathy	30	60	33	65	0.625
Previous laser photocoagulation	1	2	3	6	0.312
UAE < 200 μg/min or UACR < 30 mg/mmol or eGFR > 60 mL/min/1,73 m^2	3	6	4	8	0.511
Baseline visit	**Median/mean**	**Min-max/± SD**	**Median/mean**	**Min-max/± SD**	**p-value**
Total insulin, IU	48[b]	25–142	47[c]	23–110	0.722
Total insulin, IU/kg	0.6[d]	0.4–1.7	0.7[f]	0.4–1.1	0.341
Basal insulin, IU	21[a]	7–49	22[b]	3–56	0.542
Basal insulin, IU/kg	0.3[c]	0.1–0.6	0.3[d]	0.04–0.7	0.821
Prandial insulin, IU	26[b]	10–110	25[b]	11–59	0.908
Prandial insulin, IU/kg	0.3[d]	0.2–1.3	0.4[e]	0.1–0.7	0.654
HbA1c, mmol/mol	47[g]	33–88	48[c]	30–68	0.756
or %	6.5	5.2–10.2	6.5	4.9–8.4	
GMI, mmol/mol	47[a]	36–96	46[b]	36–66	0.949
or %	6.5	5.4–10.9	6.4	5.4–8.2	
CV, %	36[i]	19–48	35[i]	26–49	0.527
TIRp, %	59[e]	±14	62[i]	±16	0.382
TARp, %	33[c]	±16	30[h]	±18	0.482
TBRp, %	5[f]	0–34	5[j]	0–26	0.561
Weight, kg	77[b]	61–101	73[c]	57–132	0.809
BMI, kg/m^2	27[b]	21–36	28[c]	20–44	0.466

Note: The skewness of the distribution was investigated using Shapiro-Wilk test. Differences between the groups were tested with independent samples t-test or Mann-Whitney U-test.

Abbreviations: GMI = Glucose management indicator; HCL = Hybrid closed loop; isCGM = intermittently scanned continuous glucose monitoring (Libre1-2); rtCGM = real time continuous glucose monitoring; TARp = time above range for pregnancy; TBRp = time below range for pregnancy; TIRp = time in range for pregnancy; UACR = urinary albumin-to-creatinine ratio; UAE = urinary albumin excretion.

[a]missing 1.
[b]missing 2.
[c]missing 3.
[d]missing 4.
[e]missing 5.
[f]missing 6.
[g]missing 7.
[h]missing 8.
[i]missing 9.
[j]missing 10.

group the average duration of diabetes was shorter than in the metformin group (16 vs. 19 years, $p = 0.011$). There were 64 women with multiple daily injections (all on long-acting and rapid-acting insulins) and 37 on insulin pumps (all on rapid-acting insulins). A total of 21 (42%) women in the placebo group and 16 (31%) women in the metformin group had an insulin pump ($p = 0.268$). There were no differences in insulin doses or glycaemic control parameters at the baseline visit (Table 1).

3.2 | Insulin Requirements

Considering the primary outcome of the study, the change in total insulin dose (IU) (difference between baseline and third trimester maximum dose), no significant difference was found between the study groups (placebo Group 33 IU and metformin Group 27 IU, $p = 0.193$) Table 2. When analysing the primary outcome with linear regression analysis, only the baseline insulin requirement was statistically significant in predicting total insulin change during pregnancy. The mode of insulin delivery (insulin pump or multiple daily injections) or the study groups as covariates had no effect on the change in total insulin requirement.

Figure 2A–C shows the medians with lower and upper quartiles of prandial, basal and total insulin dosages in the study groups according to increasing gestational age, from baseline to the third trimester. There were no significant differences between the two groups in prandial, basal and total insulin doses at separate measurement points, and the range of the insulin doses was wide. The missing values are explained in Supporting Information S1: Figures S3–S5. In addition, insulin requirements increased similarly in both groups along with advancing gestational age in the linear mixed models (Supporting Information S1: Figures S6A–C). Missing data were random and did not relate to the studied phenomena.

However, the change in prandial insulin from baseline to the third trimester maximum dose was significantly less in the metformin group (24 and 0.3 IU/kg, 14 and 0.2 IU/kg, $p = 0.014$ and $p = 0.048$) (Table 2).

Maximum prandial insulin doses were reached at 34 weeks of gestation ($\pm$ 2 weeks) in the placebo group and at 33 weeks of gestation ($\pm$ 2 weeks) in the metformin group ($p = 0.311$). The median length of the pregnancy was similar in the two groups (37 gestational weeks) ($p = 0.760$).

In a subgroup analysis conducted as an exploratory investigation, the change from baseline to third trimester prandial insulin maximum was significantly less in the metformin group than in the placebo group among women with BMI > 25 kg/m^2 (25 vs. 15IU, $p = 0.028$) and total insulin dose > 40 IU/day at baseline (30 vs. 14 IU, $p = 0.007$ respectively) (Table 2).

3.3 | Glycaemic Control

Glycaemic control was similar between the two groups at baseline. All participants had a sensor. In both groups, 78% of the participants had isCGM and 22% rtCGM (Table 1). There were no differences between the placebo and the metformin groups in the third trimester mean or median TIRp, TARp, TBRp, HbA1c, GMI, mean sensor-derived glucose with SD and CV or the change from baseline to third trimester mean or median of the glucose parameters (Table 2). Linear mixed model analysis also showed that glycaemic control was similar between the groups throughout the pregnancy (data not shown).

3.4 | Weight Gain

There were no significant differences between the two groups in total weight gain (Table 2). Weight gain medians with lower and upper quartiles as pregnancy progressed are shown in Figure 2D. When weight gain was analysed with a linear mixed model, there were no differences between the groups (Supporting Information S1: Figure S6D). Details on the missing data of weight gain measurements are provided in Supporting Information S1: Figure S7.

However, more patients reached the BMI-adjusted weight gain target for pregnant women with type 1 diabetes in the metformin group ($n = 20$, 40%) than in the placebo group ($n = 10$, 20%) ($p = 0.029$). Table 3.

In the subgroup analysis, women in the metformin group with baseline BMI> 25 kg/m^2 and baseline total insulin dose > 40 IU/day reached the BMI-adjusted weight gain target more often ($p = 0.005$ and $p = 0.004$ respectively). Table 3.

3.5 | Pregnancy Outcome

The incidence of gestational hypertension was 4% and of preeclampsia was 12% in the placebo group and 6% and 20% in the metformin group ($p = 0.663$ and $p = 0.295$ respectively). There were no differences between the groups in the mode of the delivery: 56% in the placebo group and 61% in the metformin group delivered by caesarean section ($p = 0.626$). There were no differences in maternal outcome in the subgroups represented above.

3.6 | Neonatal Outcome

The neonatal outcomes were comparable between the two groups. The median gestational age at delivery was 37 gestational weeks in both groups ($p = 0.760$). Forty-four per cent of the deliveries were preterm (< 37^{+0} weeks of gestation) in the placebo group and 41% in the metformin group. There was one very preterm delivery (< 32^{+0} weeks of gestation) in the placebo group.

There were no differences in mean birth-weight (3795 vs. 3660 g in the placebo and metformin groups, respectively, $p = 0.256$), or in the proportions of LGA newborns (64% vs. 55%, $p = 0.352$). No SGA newborns were born in either study group.

TABLE 2 | Insulin requirement, glycaemic control, and weight in 3rd trimester and change from baseline to 3rd trimester in the metformin group and the placebo group.

	3rd trimester measurement				Change from baseline to 3rd trimester measurement			
	Placebo group $n = 50$ Median (min-max)/mean (±SD)/n (%)	Metformin group $n = 51$ Median (min-max)/mean (±SD)/n (%)	Effect size (95% Cl)[m]	p-value	Placebo group $n = 50$ Median (min-max)/mean (±SD)/n (%)	Metformin group $n = 51$ Median (min-max)/mean (±SD)/n (%)	Effect size (95% Cl)[m]	p-value
Insulin dosages								
Total (IU)[k]	82 (30–201)	74 (29–253)	7 (−6–20)	0.303	33[b] (−12–142)	27[c] (−5–186)	7 (−3–16)	0.193
Total (IU/kg)[k]	1 (0.4–2.3)	0.9[b] (0.4–2.6)	0 (−0.1–0.2)	0.450	0.3[e] (−0.3–1.5)	0.3[g] (−0.1–1.8)	0.1 (−0.1–0.2)	0.317
Basal (IU)[k]	29 (14–70)	29 (6–93)	1 (−5–6)	0.783	10[a] (−8–38)	7[b] (−3–58)	0.7 (−3–5)	0.754
Basal (IU/kg)[k]	0.4 (±0.1)	0.4[a] (±0.2)	0 (−0.1–0.1)	0.530	0.1[c] (−0.2–0.5)	0.1[d] (−0.7–0.5)	0 (0–0.1)	0.823
Prandial (IU)[k]	47 (7–150)	40 (17–180)	6 (−2–15)	0.118	24[b] (−7–115)	14[b] (−4–169)	8 (2–14)	0.014
Prandial (IU/kg)[k]	0.6 (0.1–1.7)	0.5[b] (0.3–1.8)	0.1 (−0–0.1)	0.283	0.3[d] (−0.1–1.3)	0.2[f] (−0.9–1.7)	0.1 (0–0.2)	0.048
Prandial insulin dosages in subgroups								
BMI ≤ 25 kg/m^2[k]	43 (±22)	37 (±11)	6 (−7–19)	0.340	20 (±17)	16[a] (±9)	5 (−5–15)	0.336
BMI > 25 kg/m^2[k]	59 (25–150)	45 (22–180)	8 (−5–20)	0.180	25[b] (0–115)	15[a] (−4–169)	9 (2–17)	0.028
Insulin dose ≤ 40IU[k]	39 (±15)	38 (±16)	2 (−9–12)	0.764	21 (±15)	20[b] (±17)	1 (−10–12)	0.869
Insulin dose > 40IU[k]	60 (7–150)	45 (23–180)	10 (0–23)	0.056	30[b] (−7–115)	14 (−4–169)	11 (5–20)	0.007
Glycaemic control and weight								
Mean glucose mmol/L[l]	6.8 (5.1–8.5)	6.7 (5.3–11.3)	0 (−0.4–0.4)	0.889	−0.1[a] (−9.9–1.2)	−0.1[b] (−2.6–1.2)	−0.1 (−0.4–0.2)	0.511
Mean glucose SD mmol/L[l]	2[b] (1.4–3)	1.9[a] (1.4–5)	0 (−0.1–0.2)	0.779	−0.5[i] (−4.1–0.3)	−0.3[i] (−1.3–0.5)	−0.1 (−0.3–0.1)	0.312
CV (%)[l]	30[b] (21–42)	30[b] (21–46)	0.4 (−1–2)	0.701	6[h] ± 4.7	5[i] ±4.0	1 (−2–2)	0.644
HbA1c (mmol/mol)	46[d] (±6)	46 (±8)	1 (−3–2)	0.784	4[j] (−9–31)	2[d] (−9–17)	1 (−1–4)	0.394
HbA1c (%)[l]	6.4[d] (±2.7)	6.4 (±2.9)	2 (1.8–2.4)		2.5[j] (−3–5)	2.3[d] (−3–3.7)	3 (−3–5)	
GMI (mmol/mol)[l]	45 (37–53)	46 (38–66)	0 (−2–2)	0.828	2[a] (−5–46)	1[b] (−5–12)	0.3 (−1–2)	0.599
GMI (%)[l]	6.3 (5.5–7)	6.4 (5.6–8.2)	2 (−3–3)		2.3[a] (−2.6–6.4)	2.2 (−2.5–3.2)	2 (2.5–3.4)	
TIRp (%)[l,n]	67[a] (42–88)	70[d] (19–87)	0 (−6–6)	0.918	9[e] (±12)	5[i] (±11)	4 (−1–9)	0.145
TARp (%)[l,n]	28[a] (9–56)	24[c] (8–81)	1 (−5–7)	0.668	6[c] (±14)	3[h] (±11)	3 (−2–8)	0.230
TBRp (%)[l,n]	2[a] (0–25)	4[d] (0–22)	−1 (−2–1)	0.325	1[e] (−14–28)	2[j] (−4–20)	0 (−2–2)	0.986
Weight (kg)[k]	88 (69–124)	82 (64–140)	3 (−2–8)	0.243	11[b] (±3)	10[c] (±5)	1 (−1–2)	0.363

Note: The skewness of the distribution was investigated using Shapiro-Wilk test. Differences between the groups were tested with independent samples t-test and Mann-Whitney U-test.
Abbreviations: GMI = Glucose management indicator; TARp = time above range for pregnancy; TBRp = time below range for pregnancy; TIRp = time in range for pregnancy.
[a]missing 1.
[b]missing 2.
[c]missing 3.
[d]missing 4.
[e]missing 5.
[f]missing 6.
[g]missing 7.
[h]missing 8.
[i]missing 9.
[j]missing 10.
[k]The 3rd trimester maximum value.
[l]The 3rd trimester mean value.
[m]Effect size is measured using mean difference or Hodges-Lehman estimate as appropriate.
[n]TIRp, TARp and TBRp percent sum is not 100%, because some study sites collected some TIR-values with other cut offs than instructed.

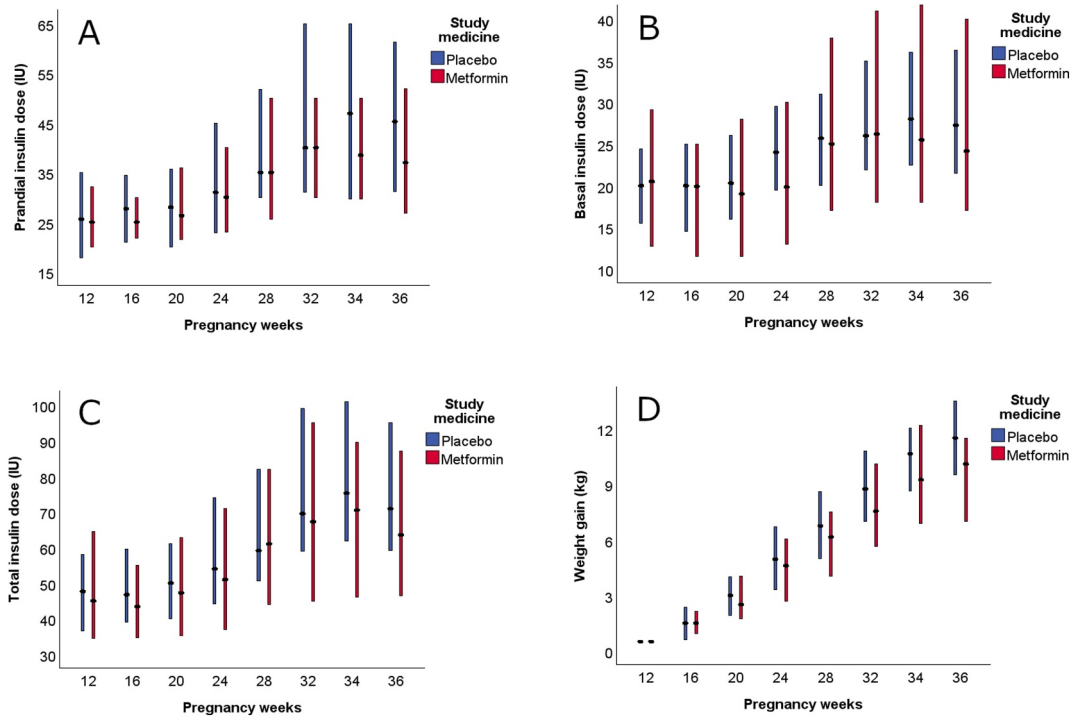

FIGURE 2 | (A–D) Prandial, basal and total insulin dose and weight gain in the placebo and metformin groups as a function of pregnancy weeks: medians with lower and upper quartiles. *N*-values of the study visits are presented in Supporting Information S1: Figures S3–S5 and S7.

The rate of neonatal intensive care admissions was similar in the study groups. There was one stillbirth in the placebo group in the 36th week of gestation. All other neonates were born in good condition. There were no differences in neonatal outcome in the subgroups represented above. More detailed information on neonatal outcome is presented in Supporting Information S1: Table S2.

3.7 | Compliance and Side-Effects

The side-effects of the study medication were comparable in both groups. Any side effects were documented in 42% of the placebo group and 51% of the metformin group ($p = 0.366$). The most common side effects were gastrointestinal symptoms: 32% in the placebo group and 49% in the metformin group (Supporting Information S1: Table S3).

Participants took the study medicine mainly as instructed. No participants were excluded due to discontinuation of study medication. Pill counts were performed on the visit at 28 gestational weeks and after delivery. Supporting Information S1: Figure S1

4 | Discussion

In this randomised, double-blind, placebo-controlled study, metformin treatment did not affect total insulin requirement, which was the primary outcome of the study. The predetermined sample size of 200 participants was not achieved. However, we showed that adding metformin to the standard insulin therapy of pregnant women with type 1 diabetes decreased prandial insulin requirement, especially in women with excess weight or with high insulin requirement at baseline. Furthermore, more women in the metformin treatment group reached the BMI-adjusted weight gain target during pregnancy and this finding was more apparent in the above-mentioned subgroups. Despite reduced prandial insulin requirements, metformin did not improve HbA1c, GMI or TIRp but had a positive effect on maternal weight gain. Although clinically relevant, these analyses were exploratory in nature and should be interpreted in the light of the study limitations.

We are unaware of any other randomised placebo-controlled trials testing the effects of metformin in pregnant women with type 1 diabetes. In GDM, the efficacy and safety of metformin have been proven in earlier studies [14]. In pregnant women with type 2 diabetes, the results of metformin studies are somewhat inconsistent. The study by Feig et al. reported findings similar to ours: insulin requirements were lower and participants gained less weight in the metformin group [9]. The study by Boggess et al. reported no beneficial effects of metformin on glycaemic control or insulin requirement [10]. In both studies, the subjects were considerably older and had higher BMI than the subjects in our study. Furthermore, the composition of the subjects, which may affect insulin resistance, was different from ours [9, 10].

Numerous studies have reported neonatal outcomes of metformin-exposed newborns in GDM and a few studies in the diabetes type 2 population. Although metformin passes to the placenta, there was no increase in the risk of congenital malformation observed in earlier studies [15]. In one study, metformin use in GDM patients was associated with an increased

TABLE 3 | Participants inside and outside the BMI adjusted weight gain target[b] during pregnancy in study groups (placebo vs. metformin).

	Placebo $n = 50$ (%)	Metformin $n = 51$ (%)[a]	Total $n = 101$[a]	OR (95% CI)
All participants $n = 101$	n (%)	n (%)	n (%)	
Weight gain in target	10 (20)	20 (40)	30 (30)	2.67 (1.09–6.52)
Weight gain outside target	40 (80)	30 (60)	70 (70)	$p = 0.029$[c]
→Over target	34 (85)	25 (83)		
→Under target	6 (15)	5 (17)		
Subgroup BMI≤ 25 n = 29[a]				
Weight gain in target	8 (57)	9 (60)	17 (59)	1.13 (0.26–4.94)
Weight gain outside target	6 (43)	6 (40)	12 (41)	$p = 0.876$[c]
→Over target	2 (33)	1 (17)		
→Under target	4 (67)	5 (83)		
Subgroup BMI > 25 $n = 71$				
Weight gain in target	2 (6)	11 (31)	13 (18)	7.79 (1.58–38.39)
Weight gain outside target	34 (94)	24 (69)	58 (82)	$p = 0.005$[c]
→Over target	32 (94)	24 (100)		
→Under target	2 (6)	0		
Subgroup insulin requirement ≤ 40 IU n = 35[a]				
Weight gain in target	8 (47)	9 (50)	17 (49)	1.13 (0.30–4.24)
Weight gain outside target	9 (53)	9 (50)	18 (51)	$p = 0.862$[c]
→Over target	7 (78)	6 (67)		
→Under target	2 (22)	3 (33)		
Subgroup insulin requirement > 40 IU n = 65				
Weight gain in target	2 (6)	11 (34)	13 (20)	8.12 (1.63–40.43)
Weight gain outside target	31 (94)	21 (66)	52 (80)	$p = 0.004$[c]
→Over target	27 (87)	19 (90)		
→Under target	4 (13)	2 (10)		

Note: Subgroups are formed from the baseline measurement of the participant.
[a]missing 1.
[b]BMI-adjusted optimal weight gain targets for pregnancies of women with diabetes type 1: BMI ≤ 25 kg/m^2 10–15 kg, 25 < BMI ≤ 30 kg/m^2 5–8 kg and BMI > 30 kg/m^2 0–5 kg (13).
[c]Pearson chi-squared test.

number of preterm deliveries [16], but a recent systematic review reported no difference in the number of preterm deliveries or gestational age at birth [14]. The risk of perinatal mortality was similar between metformin- and insulin-exposed neonates in GDM pregnancies [14]. In a recent meta-analysis, metformin-exposed newborns had lower birth weight, fewer NICU admissions and less hypoglycaemia than neonates born due to insulin-treated pregnancies [17].

In the two studies regarding type 2 diabetes, there were no differences in gestational age at delivery or rate of preterm deliveries [9, 10], but metformin use was associated with an increased proportion of SGA neonates in the study by Feig et al. In both these studies, metformin use during pregnancy showed a significant reduction in birthweight and in the proportion of LGA or extreme LGA newborns [9, 10]. In our data, there were no differences in neonatal outcome or in foetal growth pattern between the studied groups.

The role of metformin in maternal outcome has been under scrutiny. An early study showed a reduction in the rate of pre-eclampsia [18], but a later systematic review found no benefit of metformin when hypertensive complications of pregnancy were considered [19]. In our data, there were no differences between the groups in the incidence of gestational hypertension or pre-eclampsia. Also, all miscarriages occurred before randomisation.

Our results were in line with those of studies conducted with metformin therapy among non-pregnant people with type 1 diabetes. With metformin therapy, insulin requirement seems to be lower and has a positive effect on weight management [20]. In GDM, metformin is also associated with lower maternal weight gain [14]. Studies with non-pregnant patients with type 1 diabetes have not so far proven conclusively that metformin treatment reduces insulin resistance due to the heterogeneity among the few studies conducted from this point of view [20], but the declining insulin requirement with metformin treatment could point in that direction.

We estimated in our power calculations that a 15% reduction in total insulin requirement would be clinically significant. Our findings exceeded this reduction in total and prandial insulin requirements, but it is important to note that the risk of type 1 error may be increased in explorative analyses due to the small

sample size; therefore, these results should be interpreted with caution. However, the significant findings in the secondary outcomes were logical and were repeated in subgroups. Moreover, earlier studies have reported similar findings with insulin dosages and weight gain in the GDM population and in women with type 2 diabetes [9, 14, 21].

Attenuation of sharp and massive insulin dosages is of relevance because heavy insulin doses may be related to hypoglycaemic episodes between meals, necessitating carbohydrate snacks, which may in turn lead to increased weight gain and complicate insulin resistance. However, not all patients seemed to benefit from metformin, and changes in insulin doses were wide, reflecting the habitual heterogeneity of our patients coping with type 1 diabetes. In some participants, insulin requirement rose extremely high in the third trimester irrespective of the study group, which accurately reflects clinical experience with pregnancies complicated by type 1 diabetes.

It is important to note that the beneficial effects of metformin were predominantly observed in clinically insulin-resistant subgroups, namely patients who were overweight and those with a high baseline need for insulin. In fact, the effects of metformin among these patients accounted for the overall study results, whereas in leaner patients and those with a modest need for insulin, no significant difference was observed between the groups.

Mixed model analysis showed a similar third degree polynomial pattern in insulin requirement as pregnancy advanced, as has also been reported in earlier studies [6, 22, 23]. Insulin dosages increased as pregnancy progressed and metformin treatment did not cause significant changes in this trend. Neither showed differences between the groups in weight gain or glycaemic control.

The main effect of metformin has been linked to decreased nocturnal gluconeogenesis in the liver by AMP-activated protein kinase, which decreases fasting glucose. However, metformin also improves insulin sensitivity in muscles by mechanisms including insulin receptor tyrosine kinase activity, increased glycogen synthesis, and increased glucose transporter protein activity [24]. These various mechanisms in the action of metformin may explain why the main effect of our study was found in prandial rather than basal insulin requirement and why it was more pronounced in clinically insulin resistant individuals with high BMI or high insulin dosage at baseline.

Metformin may also have effects on appetite by reducing meal portions and weight gain, resulting in lower prandial insulin requirements. It is also worth noting that this is a study on metformin use in pregnancy in a patient group totally dependent on external insulin. When internal hormonal production does not align with multiple factors affecting glycaemic control, the potential effect of adjunctive metformin would be difficult to find in glycaemic control parameters.

The strength of this study is its prospective randomised, double-blind, placebo-controlled clinical setting. All the study sites are public hospitals and participants received equal treatment regardless of socioeconomic status. Insulin and medical devices (insulin pumps, catheters and sensors) are fully reimbursed in Finland. Visits to outpatient clinics and inpatient wards in hospitals are also almost fully reimbursed. All participants in the study had a type 1 diabetes diagnosis and isCGM or rtCGM. This study represents modern treatment and follow-up of pregnancies in patients with type 1 diabetes. However, at the beginning of the study in 2019, the published recommendations for glycaemic control targets during pregnancy in women with diabetes [13] were not fully available from all CGM reports. This caused some deficiencies in the glycaemic data, especially at the beginning of the study.

The main weakness of the study was the small sample size, which resulted from a slow recruitment process. We were able to recruit 2/3 of the target study sample, and 1/6 of the recruited patients were excluded from the study at randomisation or before it. The Covid pandemic and major organisational and personnel changes at our study sites had a negative effect on recruitment. Thus, the power of our study was not sufficient to test our primary hypothesis of metformin reducing total insulin change. Due to the large number of secondary outcomes, there is a possibility of chance in statistically significant findings in the present study. At most it can be stated that although the effect of metformin on total insulin change remains uncertain, it may reduce the prandial insulin requirement and may have some deterrent effect on weight gain. However, the statistically significant findings, which were logical, were supported by earlier studies and were replicated and confirmed in subgroup analysis. To study this issue thoroughly, larger studies would be needed.

Author Contributions

Elina Juuma, Kati Tihtonen, Saara E. Metso, Päivi M. Hannula Hannele Laivuori, Jukka Uotila: conceptualisation, methodology, formal analysis, investigation, resources, writing – original draft. Kati Tihtonen, Heidi Immonen, Kristiina Tertti, Leena Georgiadis, Kirsi Väyrynen, Petteri Ahtiainen, Hilkka Nikkinen, Minna Koivikko: investigation, resources. Elina Juuma, Kati Tihtonen, Saara E. Metso, Päivi M. Hannula, Mika Helminen, Kristiina Tertti, Heidi Immonen, Leena Georgiadis, Kirsi Väyrynen, Petteri Ahtiainen, Hilkka Nikkinen, Minna Koivikko, Hannele Laivuori, Jukka Uotila: writing – review and editing. Mika Helminen: formal analysis, visualisation. Hannele Laivuori and Jukka Uotila: supervision and project administration. Elina Juuma, Kati Tihtonen, Hannele Laivuori and Jukka Uotila: funding acquisition.

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Conflicts of Interest

K.T. received the study medicine (metformin and placebo) from Takeda Pharmaceuticals. E.J., S.E.M., P.M.H., K.T., H.I., L.G., K.V., P.A., H.N., M.K., H.L., M.H and J.U. report no potential conflicts of interest in connection to this article. Special thanks to our study nurses Elise Nieminen, Maria Pelander, Maija-Liisa Nikula and Kati Kuhmonen, and to all the other nurses and midwives specialised in diabetes, who helped to take care of our participants. We also want to thank Hanna Marttila, Minna Venekoski, Saara Ojala and Maiju Välimaa, who guided us through the complicated world of research legislation.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.70085.

References

1. U. Kampmann, S. Knorr, J. Fuglsang, and P. Ovesen, "Determinants of Maternal Insulin Resistance During Pregnancy: An Updated Overview," *Journal of Diabetes Research* 2019 (2019): 1–9, https://doi.org/10.1155/2019/5320156.

2. M. Y. Donath, C. A. Dinarello, and T. Mandrup-Poulsen, "Targeting Innate Immune Mediators in Type 1 and Type 2 Diabetes," *Nature Reviews Immunology* 19, no. 12 (2019): 734–746, https://doi.org/10.1038/s41577-019-0213-9.

3. S. M. Nelson, N. Sattar, D. J. Freeman, J. D. Walker, and R. S. Lindsay, "Inflammation and Endothelial Activation Is Evident at Birth in Offspring of Mothers With Type 1 Diabetes," *Diabetes* 56, no. 11 (2007): 2697–2704, https://doi.org/10.2337/db07-0662.

4. J. M. Steel, F. D. Johnstone, R. Hume, and J. H. Mao, "Insulin Requiments During Pregnancy in Women With Type 1 Diabetes," *Obstetrics & Gynecology* 83, no. 2 (1994): 253–258.

5. C. Festa, R. Fresa, N. Visalli, et al., "Insulin Requirements and Carbohydrate to Insulin Ratio in Normal Weight, Overweight, and Obese Women With Type 1 Diabetes Under Pump Treatment During Pregnancy: A Lesson From Old Technologies," *Frontiers in Endocrinology* 12 (2021): 610877, https://doi.org/10.3389/fendo.2021.610877.

6. H. A. Roeder, T. R. Moore, and G. A. Ramos, "Insulin Pump Dosing Across Gestation in Women With Well-Controlled Type 1 Diabetes Mellitus," *American Journal of Obstetrics and Gynecology* 207 (2012): 1–4, https://doi.org/10.1016/j.ajog.2012.06.029.

7. E. Wender-Ozegowska, A. Zawiejska, K. Ozegowska, et al., "Multiple Daily Injections of Insulin Versus Continuous Subcutaneous Insulin Infusion for Pregnant Women With Type 1 Diabetes," *Australian and New Zealand Journal of Obstetrics and Gynaecology* 53, no. 2 (2013): 130–135, https://doi.org/10.1111/ajo.12027.

8. G. Rena, D. G. Hardie, and E. R. Pearson, "The Mechanisms of Action of Metformin," *Diabetes* 60, no. 9 (2017): 1577–1585, https://doi.org/10.1007/s00125-017-4342-z.

9. D. S. Feig, L. E. Donovan, B. Zinman, et al., "Metformin in Women With Type 2 Diabetes in Pregnancy (Mity): A Multicentre, International, Randomised, Placebo-Controlled Trial," *Lancet Diabetes & Endocrinology* 8, no. 10 (2020): 834–844, https://doi.org/10.1016/S2213-8587(20)30310-7.

10. K. A. Boggess, A. Valint, J. S. Refuerzo, et al., "Metformin plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy: The MOMPOD Randomized Clinical Trial," *JAMA* 330, no. 22 (2023): 2182–2190, https://doi.org/10.1001/jama.2023.22949.

11. E. R. Mathiesen, "Pregnancy Outcomes in Women With Diabetes-Lessons Learned From Clinical Research: The 2015 Norbert Freinkel Award Lecture," *Diabetes Care* 39, no. 12 (2016): 2111–2117, https://doi.org/10.2337/dc16-1647.

12. L. Ringholm, S. K. Nørgaard, A. Rytter, P. Damm, and E. R. Mathiesen, "Dietary Advice to Support Glycaemic Control and Weight Management in Women With Type 1 Diabetes During Pregnancy and Breastfeeding," *Nutrients* 14, no. 22 (2022): 4867, https://doi.org/10.3390/nu14224867.

13. T. Battelino, T. Danne, R. M. Bergenstal, et al., "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range," *Diabetes Care* 42, no. 8 (2019): 1593–1603, https://doi.org/10.2337/dci19-0028.

14. K. He, Q. Guo, J. Ge, J. Li, C. Li, and Z. Jing, "The Efficacy and Safety of Metformin Alone or as an Add-On Therapy to Insulin in Pregnancy With GDM or T2DM: A Systematic Review and meta-analysis of 21 Randomized Controlled Trials," *Journal of Clinical Pharmacy and Therapeutics* 47, no. 2 (2022): 168–177, https://doi.org/10.1111/jcpt.13503.

15. S. A. Paschou, A. Shalit, E. Gerontiti, et al., "Efficacy and Safety of Metformin During Pregnancy: An Update," *Endocrine* 83, no. 2 (2024): 259–269, https://doi.org/10.1007/s12020-023-03550-0.

16. J. A. Rowan, E. C. Rush, V. Obolonkin, M. Battin, T. Wouldes, and W. M. Hague, "Metformin in Gestational Diabetes: The Offspring Follow-Up (Mig TOFU) - Body Composition at 2 Years of Age," *Diabetes Care* 34, no. 10 (2011): 2279–2284, https://doi.org/10.2337/dc11-0660.

17. B. Sheng, J. Ni, B. Lv, G. Jiang, X. Lin, and H. Li, "Short-Term Neonatal Outcomes in Women With Gestational Diabetes Treated Using Metformin Versus Insulin: A Systematic Review and meta-analysis of Randomized Controlled Trials," *Acta Diabetologica* 60, no. 5 (2023): 595–608, https://doi.org/10.1007/s00592-022-02016-5.

18. A. Syngelaki, K. H. Nicolaides, J. Balani, et al., "Metformin Versus Placebo in Obese Pregnant Women Without Diabetes Mellitus," *New England Journal of Medicine* 374, no. 5 (2016): 434–443, https://doi.org/10.1056/NEJMoa1509819.

19. A. Alqudah, M. C. McKinley, R. McNally, et al., "Risk of Pre-Eclampsia in Women Taking Metformin: A Systematic Review and Meta-Analysis," *Diabetic Medicine* 35, no. 2 (2018): 160–172, https://doi.org/10.1111/dme.13523.

20. Y.-S. Liu, C.-N. Chen, Z.-G. Chen, Y. Peng, X.-P. Lin, and L.-L. Xu, "Vascular and Metabolic Effects of Metformin Added to Insulin Therapy in Patients With Type 1 Diabetes: A Systematic Review and Meta-Analysis," *Diabetes/Metabolism Research and Reviews* 36, no. 6 (2020): e3334, https://doi.org/10.1002/dmrr.3334.

21. C. Liu, D. Wu, X. Zheng, P. Li, and L. Li, "Efficacy and Safety of Metformin for Patients With Type 1 Diabetes Mellitus: A meta-analysis," *Diabetes Technology & Therapeutics* 17, no. 2 (2015): 142–148, https://doi.org/10.1089/dia.2014.0190.

22. A. García-Patterson, I. Gich, S. B. Amini, P. M. Catalano, A. De Leiva, and R. Corcoy, "Insulin Requirements Throughout Pregnancy in Women With Type 1 Diabetes Mellitus: Three Changes of Direction," *Diabetologia* 53, no. 3 (2010): 446–451, https://doi.org/10.1007/s00125-009-1633-z.

23. G. Ø Skajaa, J. Fuglsang, U. Kampmann, and P. G. Ovesen, "Parity Increases Insulin Requirements in Pregnant Women With Type 1 Diabetes," *Journal of Clinical Endocrinology and Metabolism* 103, no. 6 (2018): 2302–2308, https://doi.org/10.1210/jc.2018-00094.

24. R. Herman, N. A. Kravos, M. Jensterle, A. Janež, and V. Dolžan, "Metformin and Insulin Resistance: A Review of the Underlying Mechanisms Behind Changes in GLUT4-Mediated Glucose Transport," *International Journal of Molecular Sciences* 23, no. 3 (2022): 1264, https://doi.org/10.3390/ijms23031264.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: dmrr70085-sup-0001-suppl-data.docx.