

Supplemental Material

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Table S1 Maternal and neonatal outcomes in the metformin group who delivered a small for gestational age (SGA) infant and those in the placebo group who delivered a small for gestational age (SGA) infant and meeting the <5th centile using the Kramer growth curves.

	SGA Metformin	SGA Placebo	P Value
n	21	10	
Preeclampsia (%)	7 (33.3)	5 (50)	0.620
Worsening Chronic Hypertension	3 (14.3)	2 (20.0)	1.00
Cesarean Section (%)	10 (47.6)	7 (70.0)	0.433
Insulin u/kg/day at 34-36 weeks GA (median [IQR])	0.71 [0.54, 1.05]	1.55 [1.16, 1.99]	0.065
Gestational age, weeks (mean (SD))	37.4 (2.3)	35.4 (3.5)	0.058
Birthweight, g (mean (SD))	2276 (495)	1874 (738)	0.082
Birthweight z-score (mean (SD))*	-1.22 (0.63)	-1.73 (0.94)	0.082
GROW z-score**	-2.27 (0.74)	-2.60 (1.09)	0.322
Sum of skinfolds, mm (median [IQR])	12.4 [10.3, 14.2]	15.0 [11.6, 22.9]	0.422
Head Circumference, cm (mean (SD))	31.7 (3.2)	30.6 (3.5)	0.427
Abdominal Circumference, cm (mean (SD))	29.1 (3.0)	28.8 (3.4)	0.850
Composite outcome present (%)⁺	7 (33.3)	8 (80)	0.041
Pre-term Birth (%)	5 (23.8)	6 (60)	0.117
NICU admission >24 hours (%)	4 (19.0)	5 (55.6)	0.118
Neonatal Hypoglycemia (%)	3 (15.0)	3 (33.3)	0.339

*Using Kramer growth curves⁹

** Using GROW growth charts (gestation- related optimal weight) that adjust infant birthweight for maternal parity, ethnicity, height, and weight, and for infant sex and gestational age. (Holmes VA, Young IS, Patterson CC, et al. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care* 2011; **34**: 683–88.)

⁺ Composite outcome includes preterm birth, birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycaemia, and NICU admission lasting >24 hours

Table S2A Univariate and Multivariable Models for Small for Gestational Age.

Table S2A Univariate models

Variable	OR	95% CI	P-value
Nephropathy	3.29	1.24, 7.88	0.011
Chronic hypertension	3.04	1.56, 5.82	<0.001
Metformin use during trial	2.11	1.12, 4.14	0.024
Pre-pregnancy BMI (per 5 points)	0.86	0.68, 1.07	0.200
Smoking during pregnancy	0.56	0.13, 1.62	0.347
First HbA1c (per 1%)	1.02	0.84, 1.22	0.815

Table S2B Multivariable model

Variable	OR	95% CI	P-value
Nephropathy	2.94	1.05, 7.49	0.029
Chronic hypertension	2.81	1.40, 5.50	0.003
Metformin	2.33	1.21, 4.67	0.013

Table S2C Model with comorbid variable (Chronic hypertension and/or Nephropathy)

Variable	OR	95% CI	P-value
Chronic hypertension and/or Nephropathy	3.05	1.58, 5.81	<0 .001
Metformin	2.26	1.19, 4.47	0.016

Table S2D Model with Interaction of treatment and comorbidity

Variable	OR	Lower 95%	P-value
Chronic hypertension and/or Nephropathy in non-metformin group	3.01	1.01, 8.80	0.043
Metformin in non-comorbid group	2.24	0.98, 5.58	0.067
Interaction term (metformin and comorbidity)	1.02	0.27, 3.96	0.975

Table S3 Multivariable model with comorbid condition, treatment with metformin and late pregnancy: predictors of small for gestational age infants using logistic regression.

	OR	95% CI	P-Value
Comorbidity (nephropathy and/or chronic hypertension)	2.11	1.09, 4.00	0.024
Treatment with metformin during trial	1.87	0.98, 3.72	0.064
Final HbA1c (per 1%)	0.48	0.27, 0.81	0.009
Weight gain below IOM criteria	1.14	0.52, 2.33	0.739

Table S4A Mean glucose levels throughout pregnancy and by trimester in mmol/l, according to birthweight category group (placebo and metformin).

	SGA	AGA	LGA	P value
n	45	290	125	
Mean Glucose /Day (mean (SD))	5.89 (0.69) (106 mg/dl)	6.04 (0.85) (109 mg/dl)	6.48 (1.06) (116 mg/dl)	<0.001
Mean Glucose in Trimester 1 (mean (SD))	5.99 (0.77) (108 mg/dl)	6.01 (1.05) (108 mg/dl)	6.55 (1.22) (118 mg/dl)	0.061
Mean Glucose in Trimester 2 (mean (SD))	5.95 (0.80) (107 mg/dl)	6.02 (0.92) (108 mg/dl)	6.44 (1.13) (116 mg/dl)	0.001
Mean Glucose in Trimester 3 (mean (SD))	5.77 (0.53) (104 mg/dl)	6.03 (0.80) (109 mg/dl)	6.55 (0.93) (118 mg/dl)	<0.001

LGA=large for gestational age, AGA=appropriate for gestational age, SGA=small for gestational age

Table S4B Mean glucose levels throughout pregnancy and by trimester in mmol/l, according to treatment group (placebo and metformin) in the small for gestational age infants.

	SGA* Metformin	SGA* Placebo	p
n	30	15	
Mean Glucose /Day (mean (SD))	5.77 (0.70) (104 mg/dl)	6.17 (0.59) (111 mg/dl)	0.090
Mean Glucose in Trimester 1 (mean (SD))	5.68 (0.44) (102 mg/dl)	6.37 (0.95) (115 mg/dl)	0.111
Mean Glucose in Trimester 2 (mean (SD))	5.78 (0.80) (104 mg/dl)	6.31 (0.70) (114 mg/dl)	0.055
Mean Glucose in Trimester 3 (mean (SD))	5.74 (0.56) (103 mg/dl)	5.83 (0.45) (105 mg/dl)	0.633

*SGA = small for gestational age

Figure S1 Mean glucose (mmol/l) over 3 trimesters by treatment (metformin or placebo) and neonatal size: small for gestational age (SGA), appropriately grown for gestational age (AGA), and large for gestational age (LGA).

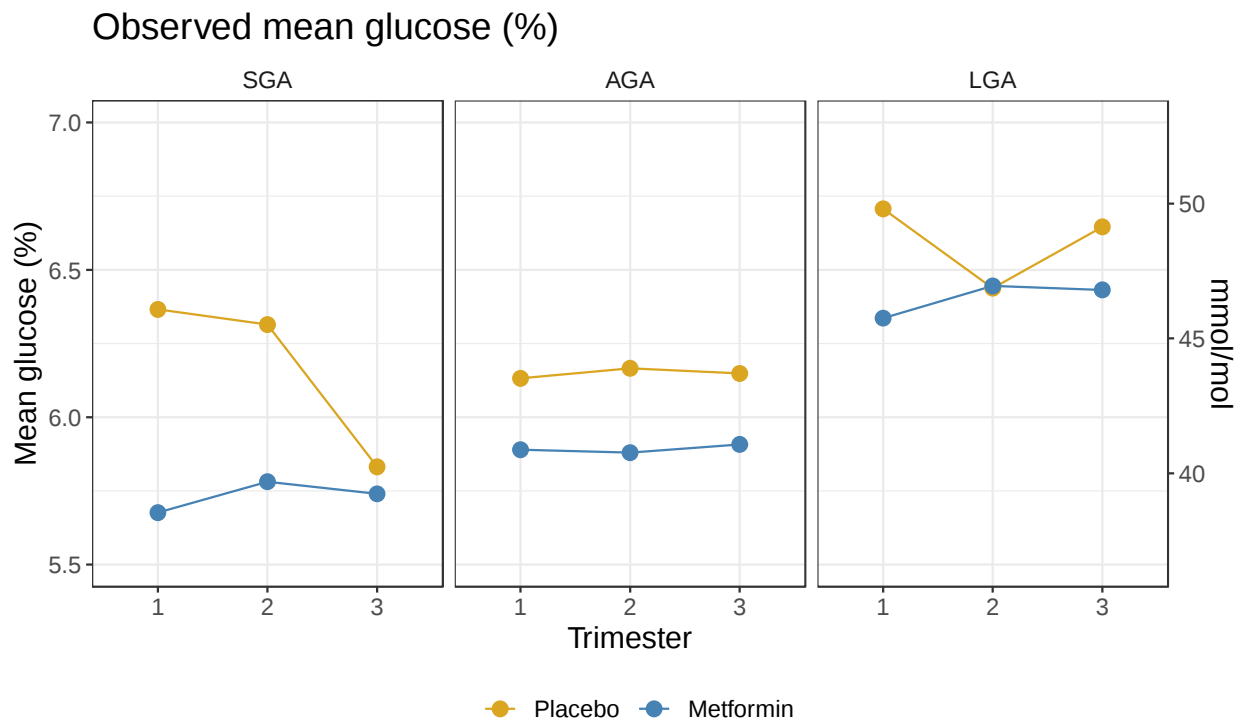
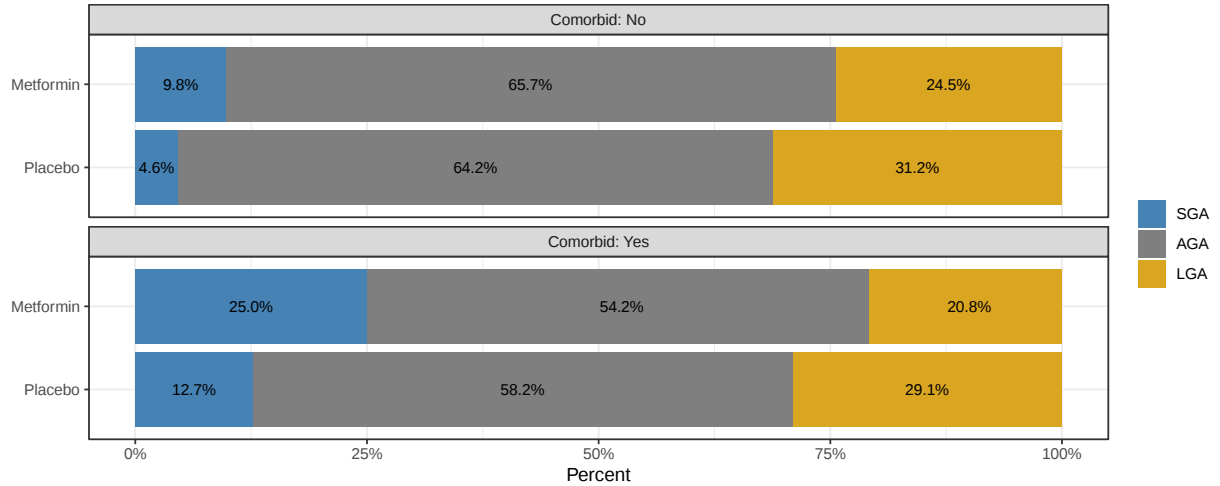


Figure S2: Percentages of small for gestational age (SGA), appropriately grown for gestational age (AGA), and large for gestational age (LGA), with and without metformin, in those with and without a comorbid condition (nephropathy and/or chronic hypertension), referred to here as Comorbid:yes and Comorbid:no.



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