Early Metformin in Gestational Diabetes A Randomized Clinical Trial

JAMA | Original Investigation

JAMA. doi:10.1001/jama.2023.19869 Published online October 3, 2023.

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- GDM : carbohydrate intolerance resulting in hyperglycemia with onset during pregnancy
- increased risk : **weight gain, cesarean , preeclampsia**, increased risk of **NICU** admission (eg, birth injuries and respiratory distress)
- pregnant individuals and their offspring are at increased **longterm risk of type 2 diabetes**

- gestational diabetes initially manage with **MNTand exercis**e
- pharmacotherapy is required, insulin is recommended
- Insulin is effective in improving of several perinatal outcomes but is associated with increased rates of **maternal and infant hypoglycemia, excess gestational weight gain, higher rates of cesarean birth, treatment in a neonatal intensive care unit**

Metformin

- associated with improved maternal and fetal metabolic outcomes, concerns about a **higher rate of spontaneous preterm birth** and **small for gestational age have been reported.**
- crosses the placenta and activates AMP-activated protein kinase, which leads to regulate placental amino acid transport
- Routine earlier initiation of metformin (at the time of diagnosis) may **improve glycemic** control, **reduce the need for insulin therapy**, may have clinical advantages beyond glycemic control, such as **reducing gestational weight gain**

Methods

Trial Design and Oversight

- Effectiveness of early metformin in addition to usual care in the reduction of gestational diabetes effects (EMERGE), was a phase 3, parallel, superiority, randomized, double-blind, placebo-controlled trial of metformin introduced **at the time of gestational diabetes diagnosis and continued until delivery**
- **conducted at 2 sites in Ireland**—a tertiary university hospital referral center (average annual birth rate, 2800) and a smaller regional hospital(average annual birth rate, 1600)

Methods

Trial Population

- aged 18 to 50 years
- according to WHO 2013 criteria(any one of the following glucose values: **fasting ≥92** mg/dl, **1 hour ≥180** mg/ dl, or **2 hour≥ 153** mg/dl), were pregnant with a singleton fetus (confirmed by scan) with a **gestation up to 28 weeks (+ 6 days)**
- **Exclusion criteria** included an **established diagnosis of diabetes** (type 1, type 2, monogenic or secondary), **a fasting glucose level of 126 mg/dl or greater** or a **2-hour value of 200 mg/dl on the OGTT** (8-oz solution with 75 grams of sugar), or a known intolerance to metformin.

Methods

Trial Procedures

- Randomly on a 1:1 ratio to receive either placebo or metformin, in addition to usual care
- A minimization strategy was used to balance proportion of participants with a BMI of less than or equal to 30 vs greater than 30 and a history of gestational diabetes between groups.
- Treatment allocation was **masked** from site investigators, site personnel, participants, and outcome assessors.
- Usual care consisted of standardized advice on MNT and exercise

Methods

Trial Procedures

- Participants performed daily **7-point glucose testing** at meal time (before and 1 hour after) and before bed and were seen by a clinician at an antenatal diabetes clinic at **2- to 4-week interval**s.
- Metformin was started at 500 mg daily, and titrated upwards every 2 days over 10 days, to a maxi mum of(5 tablets) in 2 doses (1500 mg in the morning and 1000 mg in the evening), taken until delivery
- Significant adverse effects were advised to reduce their dose to the maximum tolerated dose
- **Insulin was started : 2 or more home glucose readings between clinic visits were outside the prespecified glucose targets (fasting level, ≤92; 1-hour postprandial level, ≤126)** and could not be explained by transient factors such as sleep, stress, or infection
- The dosing of insulin was based on maternal weight and gestational week of initiation
- If insulin was initiated, study medication was continued.

Methods

Trial Procedures

- Laboratory tests were performed (eg, **hemoglobin A1C and fasting blood glucose**) at gestational **weeks 32 and 38** (plus or minus 1 week was permitted for testing time)
- The Diabetes Treatment Satisfaction Questionnaire was completed at study week 12
- drug pill counting was completed every 4 weeks to measure adherence in the previous 4-week time period. If medication was discontinued, it was recorded as 0 for that time period
- A birth visit occurred within 72 hours after delivery to determine maternal and fetal outcomes
- Participants were contacted by phone at 4 weeks and in person at 12 weeks after delivery

Outcomes

- **Primary outcome**, determined at the time of infant delivery, was **a composite of insulin initiation (before delivery) or a fasting laboratory blood glucose value of 92 or greater at week 32 or week 38 of gestation.**
- There were 12 prespecified secondary outcomes
- **Secondary maternal outcomes** were time to insulin initiation, insulin dose required, development of pregnancy-induced hypertension or preeclampsia, antepartum and postpartum hemorrhage, any bleeding, mode and time of delivery with determination of numbers with preterm birth before 37 weeks of gestation, gestational weight gain from randomization to delivery and from randomization to 12 weeks' postpartum, self-reported capillary glycemic control, and treatment satisfaction.

- **<u>Secondary neonatal outcomes</u>** included infant birth weight, length, and head circumference with derived measures for **large for gestational age** above the 90th percentile, **small for gestational age** below the 10th percentile, **macrosomia greater than 4 kg, low birth weight less than 2.5 kg**, proportion of infants with neonatal morbidities including need for neonatal **intensive care,** respiratory distress requiring respiratory support, jaundice requiring phototherapy, major congenital anomalies, Apgar score less than 7 at 5 minutes, and neonatal hypoglycemia

Statistical Analysis

- Difference between placebo and metformin for the primary outcome was assessed for statistical significance at **α less than .05 using a z test** for 2 independently estimated proportions.
- **Treatment effects** were expressed as **risk ratios (RRs)** with 95% CIs calculated using the delta method
- All analyses were completed using R-package, version 4.1.2

Results

Participants

- From June 2017 to September 2022, after screening 2308 pregnancies with gestational diabetes resulted, 535 pregnancies (in 510 participants) underwent randomization (268 to metformin and 267 to placebo)
- At randomization, maternal characteristics were similar between groups

Figure 1. Flow of Patients With Gestational Diabetes Randomized to Metformin vs Placebo

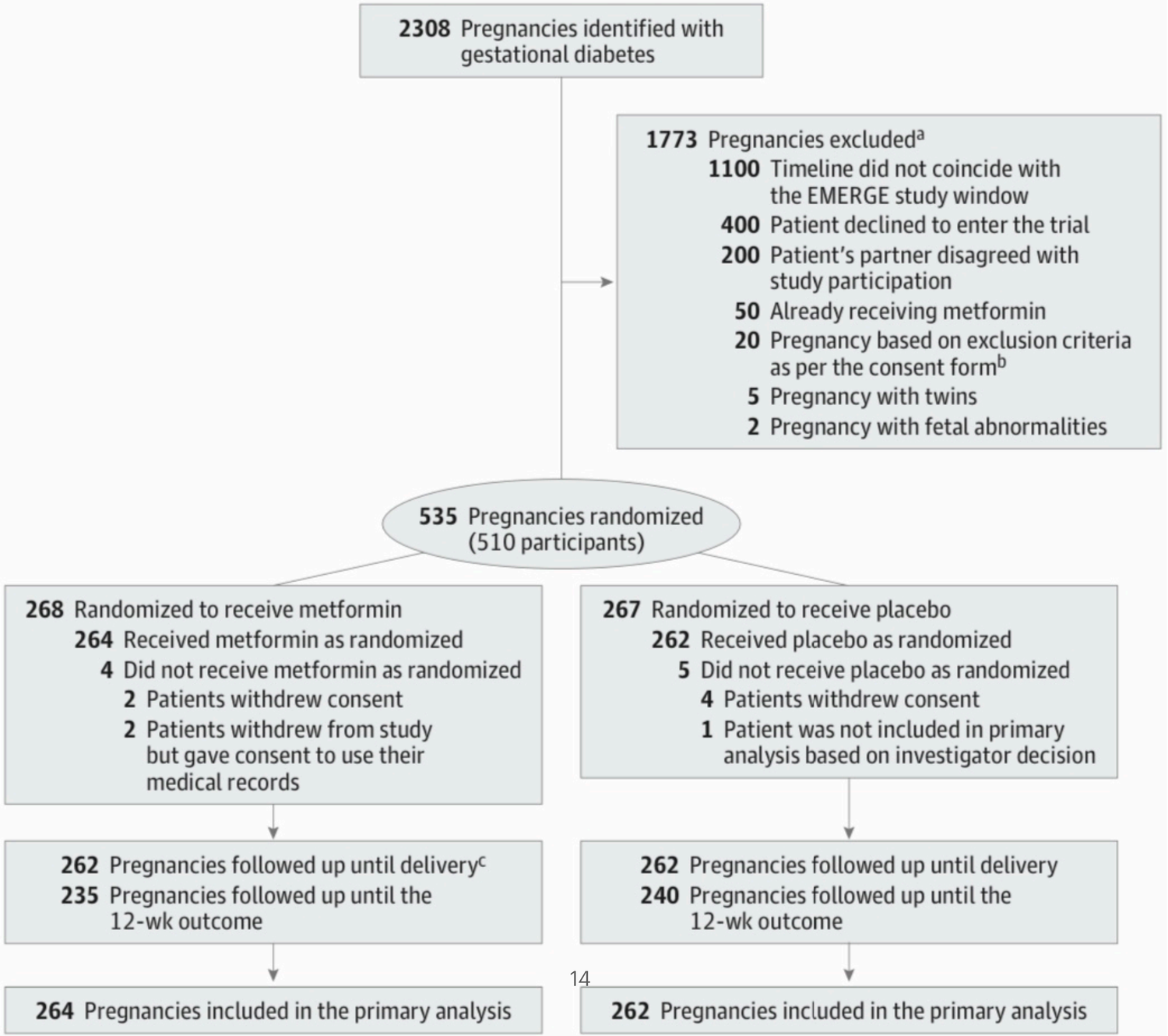

Table 1. Maternal Characteristics at Baseline

Variable	Early metformin (n = 268)[a]	Placebo (n = 267)[a]
Demographic characteristics		
Age, mean (SD), y	34.3 (4.9)	34.3 (4.7)
Racial or ethnic group[b]		
African/Black	7 (2.6)	6 (2.2)
Asian	17 (6.3)	29 (10.9)
Irish Traveller	11 (4.1)	2 (0.7)
White	219 (81.7)	209 (78.3)
Other	14 (5.2)	21 (7.9)
Highest level of education	(n = 268)	(n = 266)
Tertiary	214 (79.9)	220 (82.7)
Secondary	45 (16.8)	43 (16.2)
Primary	9 (3.4)	3 (1.1)
In receipt of medical card, No./total (%)[c]	63/268 (23.5)	63/266 (23.7)
Private health insurance, No./total (%)[c]	126/268 (47)	116/266 (43.6)
Unemployed, No./total (%)	19/268 (7.1)	27/266 (10.2)
Past history		
Smoking during pregnancy	17 (6.3)	17 (6.4)
Prior hypertension	12 (4.5)	4 (1.5)
Nulliparous	63 (23.5)	64 (24)
Previous obstetrical history available, No./total (%)[d]	181/205 (88.3) [n = 181]	172/203 (84.7) [n = 172]
Cesarean delivery	70 (38.7)	74 (43)
Gestational diabetes	65 (35.9)	65 (37.8)
Infant with birth weight >4000 g	57 (31.5)	44 (25.6)
Postpartum hemorrhage	28 (15.5)	20 (11.6)
Preeclampsia	24 (13.3)	23 (13.4)
Antepartum hemorrhage	20 (11)	15 (8.7)
Infant with congenital anomaly	13 (7.2)	13 (7.6)
Previous stillbirth	2 (1.1)	2 (1.2)

Abbreviation: BMI, body mass index.

Conventional unit conversion factor: to convert glucose to mg/dL, divide by 0.0555.

[a] Numeric values are reported as No. (%) unless otherwise indicated.

[b] Ethnic groups were collected in a closed form. Individuals accounted under the category of *Other* include the following: Afghan, 3; Bangladeshi, 3; Brazilian, 8;

Physical findings		
BMI at enrollment, median (IQR)[e]	29.9 (25.6-33.7)	30 (26.6-34.3)
BMI <30, No./total (%)[e]	131/255 (51.4)	121/251 (48.2)
BMI ≥30, No./total (%)[e]	124/255 (48.6)	130/251 (51.8)
Gestation at randomization, median (IQR), wk	27 (25.7-28)	27 (25.6-28)
Duration from randomization to delivery, mean (SD), wk	13.7 (4.7)	13.6 (4.3)
Duration from randomization to delivery, median (IQR), wk	12.3 (11-14.1)	12.4 (11.1-14.2)
Systolic blood pressure at randomization, mean (SD), mmHg	114.9 (9.5)	114.4 (9.2)
Diastolic blood pressure at randomization, mean (SD), mmHg	68.9 (8)	68.7 (8.8)
Laboratory findings		
Results of 75 g oral glucose tolerance, mean (SD), mmol/L		
Plasma glucose level after overnight fast	5.2 (0.5)	5.2 (0.5)
Postprandial plasma glucose level at 1 h	9.4 (1.9)	9.7 (1.9)
Postprandial plasma glucose level at 2 h	7.1 (1.6)	7.1 (1.6)
Hemoglobin A_{1c} at randomization, mean (SD), mmol/mol[f]	33 (3.4) [n = 266]	32.9 (3.5) [n = 265]

Results

Primary Efficacy Outcome

- Among 150 participants (56.8%) in the metformin group and 167 participants (63.7%) in the placebo group, there was no statistically significant difference in the **primary composite outcome of insulin initiation or fasting glucose level** of 92mg/dL or greater at gestational weeks 32 or 38 (risk ratio, 0.89 [95% CI, 0.78-1.02]; P = .13)
- **Insulin initiation** occurred in 101 participants (38.4%) in the metformin and 134 (51.1%) in the placebo groups (relative risk, 0.75; 95% CI 0.62-0.91; P = .004)

Table 2. Maternal Outcomes

Outcome	No./total (%)[a] Early metformin (n = 264)	Placebo (n = 262)	Risk difference (95% CI)	Relative risk (95% CI)	*P* value
Primary outcome[b]					
Primary composite outcome	150/264 (56.8)	167/262 (63.7)	−6.9% (−15.1% to 1.4%)	0.89 (0.78 to 1.02)	.13
Initiation of insulin only	101/263 (38.4)	134/262 (51.1)	−12.7% (−21.2% to −4.3%)	0.75 (0.62 to 0.91)	.004
Fasting glucose at wk 32, mean (SD), mmol/L	4.9 (0.5)	5.0 (0.5)	−0.1 (−0.19 to −0.01)		.03
Fasting glucose at wk 38, mean (SD), mmol/L	4.5 (0.4)	4.7 (0.5)	−0.2 (−0.28 to −0.09)		<.001
Secondary outcomes					
Time to insulin initiation[c]					.001
Mode of delivery					
Cesarean delivery	114/262 (43.5)	100/262 (38.2)	5.2% (−3.1% to 13.7%)	1.14 (0.93 to 1.4)	.40
Induced delivery	75/262 (28.6)	88/262 (33.2)	−4.6% (−12.5% to 3.3%)	0.86 (0.67 to 1.11)	
Spontaneous delivery	73/262 (27.9)	75/262 (28.6)	−0.7% (−8.5% to 6.9%)	0.97 (0.74 to 1.28)	
Emergency cesarean	53/114 (46.5)	53/100 (53)	−6.5% (−13.9% to 12.9%)	0.99 (0.74 to 1.32)	1
Elective cesarean	61/114 (53.5)	47/100 (47)			
Preterm birth (<37 wk)	24/261 (9.2)	17/260 (6.5)	2.8% (−2.0% to 7.3%)	1.41 (0.78 to 2.56)	.33
Hemoglobin A_{1C} at wk 38, mean (SD), mmol/mol	33.9 (3.4)	35.0 (3.9)	−1.1% (−1.79 to −0.34)		.004
Insulin dose required, mean (SD), IU	20.4 (19.8)	24.2 (22.8)	−3.8 (−9.3 to 1.7)		.17
Maternal weight change randomization to delivery, mean (SD), kg	0.8 (3.3)	2.0 (3.6)	−1.2 (−1.99 to −0.42)		.003
Maternal weight change randomization to wk 12 postpartum, mean (SD), kg	−5.9 (4.4)	−5.1 (4.9)	−0.8 (−1.64 to 0.06)		.07
Treatment satisfaction	173/227 (76.2)	159/237 (67.1)	9.1% (1.0% to 17.0%)		.04
Maternal morbidity[d]					
Gestational hypertension	31/262 (11.8)	28/262 (10.6)	1.2% (−4.2% to 6.6%)	1.11 (0.69 to 1.8)	.77
Preeclampsia	10/262 (3.8)	5/262 (1.9)	1.9% (−0.9% to 4.8%)	2.01 (0.7 to 5.79)	.29
Antepartum hemorrhage	15/262 (5.7)	27/262 (10.3)	−4.6% (−9.2% to 0.1%)	0.56 (0.3 to 1.02)	.08
Postpartum hemorrhage	51/262 (19.5)	63/262 (24.0)	−4.5% (−11.6% to 2.5%)	0.81 (0.59 to 1.12)	.24
Any bleeding	60/262 (22.9)	80/262 (30.5)	−7.6% (−15.2% to −0.1%)	0.75 (0.56 to 1.0)	.06

Conventional unit conversion factor: to convert glucose to mg/dL, divide by 0.0555.

[a] Numeric values are reported as No./total (%) unless otherwise indicated.

[b] The composite primary outcome was achieved if a participant initiated insulin treatment during the period between randomization and delivery or had a measured fasting glucose level of at least 5.1 mmol/mol at 32 weeks' gestation or at 38 weeks' gestation.

[c] Only a *P* value is shown for this row because it is not possible to calculate average or median survival times due to the censoring in the distribution (eg, the time to insulin would be censored at the delivery date for more than 50% of the metformin group).

[d] Other outcomes related to maternal morbidity are detailed in eTable 2 in Supplement 2.

Figure 2. Time to Insulin Initiation and Fasting Blood Glucose Between Metformin and Placebo Groups

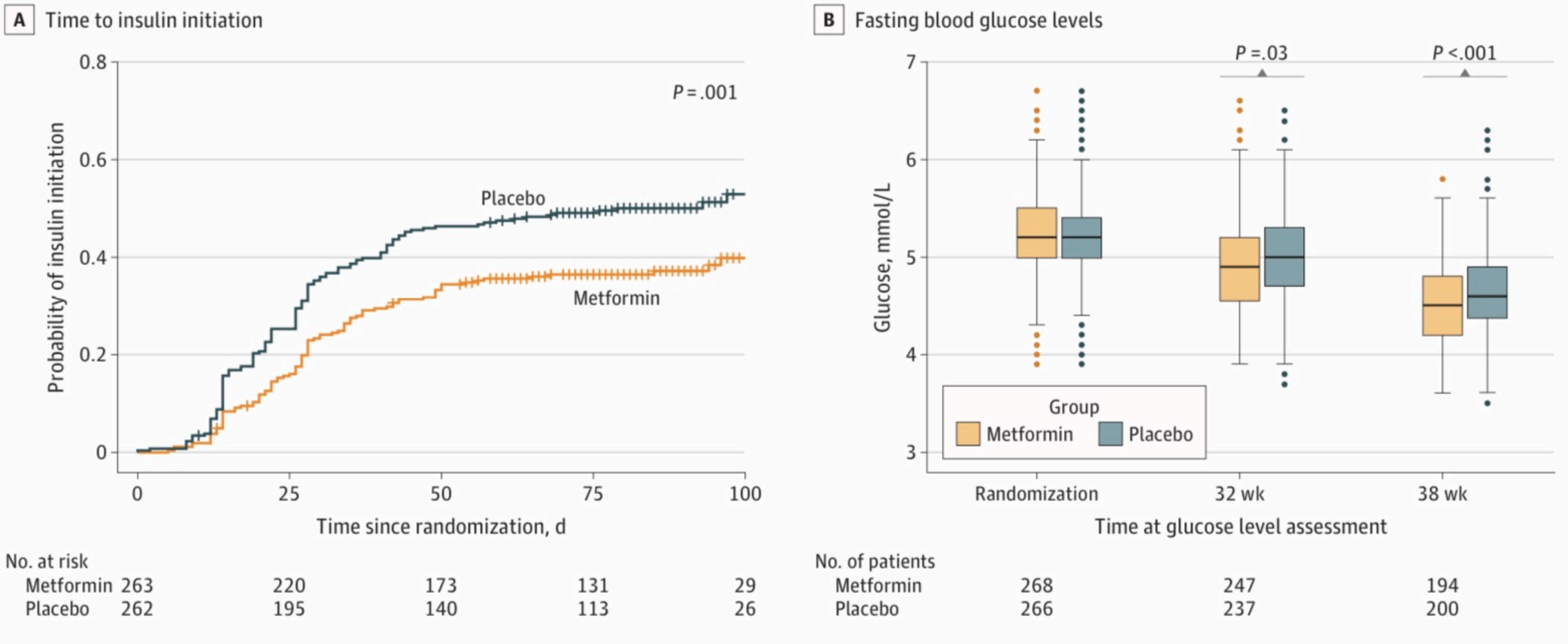

Table 3. Neonatal Weight, Height, and Size

Outcome	No./total (%)[a]		Unadjusted risk difference (95% CI)	Unadjusted relative risk (95% CI)	*P* value[b]	*P* value[c]
	Metformin (n = 262)	Placebo (n = 262)				
Neonatal size						
Gestational age at birth, mean (SD), wk[d]	39.1 (1.5)	39.1 (1.6)	0 (−0.3 to 0.2)		.66	
Birth weight, mean (SD), g	3393 (527)	3506 (510)	−113 (−201 to −24)		.01	.005
Birth weight >4000 g	20/262 (7.6)	39/262 (14.8)	−7.2% (−12.6% to −1.8%)	0.5 (0.3 to 0.9)	.02	.02
Birth weight >90th percentile	17/261 (6.5)	39/261 (14.9)	−8.4% (−13.7% to −3.2%)	0.4 (0.3 to 0.8)	.003	
Birth weight <2500 g	16/262 (6.1)	9/262 (3.4)	2.7% (−1% to 6.3%)	1.8 (0.8 to 4.0)	.12	.12
Birth weight <10th percentile	15/261 (5.7)	7/261 (2.7)	3.0% (−0.4% to 6.5%)	2.1 (0.9 to 5.2)	.13	
Head circumference, mean (SD) [No.], cm	34.7 (1.6) [253]	34.7 (1.8) [253]	0 (−0.3 to 0.3)		.82	.60
Crown-heel length, mean (SD) [No.], cm	51.0 (3.2) [253]	51.7 (3.3) [253]	−0.7 (−1.3 to −0.2)		.02	.02
Abdominal circumference, mean (SD) [No.], cm	33.4(2.4) [154]	33.3 (2.8) [157]	0.1 (−0.5 to 0.7)		.72	.81
Mid-upper-arm circumference, mean (SD) [No.], cm	11.0 (1.0) [154]	11.1 (1.1) [156]	−0.1 (−0.3 to 0.1)		.47	.33
Ponderal index mean, mean (SD) [No.][e]	2.6 (0.4) [253]	2.6 (0.5) [253]	0 (−0.1 to 0.1)		.68	
Neonatal morbidities[f]						
Need for NICU care	41/262 (15.6)	33/262 (12.6)	3% (−2.9% to 9%)	(0.8 to 1.9)	.38	
Respiratory distress requiring respiratory support	24/262 (9.2)	18/262 (6.9)	2.3% (−2.4% to 6.9%)	1.3 (0.7 to 2.4)	.42	
Jaundice requiring phototherapy	1/262 (0.4)	0	0.4% (−.4% to 1.1%)		>.99	
Major congenital anomalies	10/262 (3.8)	7/262 (2.7)	1.1% (−1.9% to 4.2%)	1.5 (0.6 to 3.7)	.62	
Apgar score <7 at 5 min	1/262 (0.4)	1/260 (0.4)	0% (−1% to 1%)	1 (0.1 to 15.8)	>.99	
Neonatal hypoglycemia (<2.6 mmol/L on ≥1 occasion <60 min postdelivery)	36/262 (13.7)	34/262 (13)	0.7% (−5.1% to 6.6%)	1.1 (0.7 to 1.6)	.90	

Discussion

- This randomized clinical trial **did not confirm** statistical superiority of early metformin over placebo for the **primary outcome, a composite of insulin initiation or a fasting blood glucose level of 5.1 mmol/L or greater at gestational week 32 or 38 between groups.**

Discussion

- The **decreased proportion of large for gestational age** infants or **infants weighing more than 4000 g** in participants randomized to early metformin is consistent with **previous clinical trials.**
- **Minimizing excessive intrauterine growth** reduces increased risks of diabetes, obesity, and hypertension in adulthood
- increase in the proportion of infants weighing less than 2500 g or small for gestational age may contribute to a **reduction in lean body mass.**
- decrease in crown-heel length in the metformin group may reflect an adverse effect on lean body mass, which may have a potential for long-term adverse consequence in terms of future adiposity
- a previous systematic review has identified overweight or obesity in metformin- exposed children.

Discussion

- support benefits of metformin **on maternal weight gain**, has been reported in **previous clinical trials**. Lower weight gain in the metformin group is likely to be due to less insulin use and a direct effect of metformin on food intake
- Prior studies report significant associations of gestational glycemic control and weight gain with **future risk of diabetes and cardiovascular disease.**
- Medium- and long- term **maternal follow-up of this cohort has begun** to assess if early use of metformin has long-term maternal cardio- metabolic benefits.

Discussion

- proportion of participants **requiring insulin in the metformin group** was **lower** than observed in metformin- exposed women in the **MiG trial**
- this likely reflects the **ethnic** and **BMI differences** between the trials as MiG enrolled a broader ethnic group with a greater mean BMI than EMERGE.
- In addition, participants randomized in EMERGE had a **gestational diabetes diagnosis** based on WHO 2013 criteria, which are **lower** than the criteria used in the MiG trial.

Discussion

- Metformin is considered a suitable first-line therapy by NIH and Care Excellence guideline recommendations, the American Diabetes Association does not consider metformin as first-line therapy, **particularly in pregnant individuals with hypertension or pre- eclampsia or those at risk for intrauterine growth restriction.**

strengths

- Participants across **all BMI categories were included**, and 50% of participants had a BMI of less than 30, a participant category that has not been well-represented in other gestational diabetes clinical trials. Based on this spread of BMI across all categories, the **results of this trial may have greater generalizability.**

Limitations

- First , the trial took **longer to complete** than originally planned due to the **COVID-19 pandemic**, and trial duration was affected **by 2 cyber attacks** which created logistical challenges but did not impact, influence, or compromise any EMERGE data).
- Second, 80% of the participants were White European individuals, reflective of the Irish population. The **lack of a larger ethnic mix** may have limited broad generalizability for other races or ethnicities.

- Third, we employed the **WHO 2013 gestational diabetes diagnostic criter**ia, which are widely used in Europe, Australia, and Asia but not in other regions of the world. For example the **2-step** Carpenter and Coustan criteria are more widely used in the US, potentially limiting generalizability of this study's findings.
- Fourth, our management approach included implementation of **tight glucose control** (fasting glucose <5.1 mmol/L) and s**trict insulin initiation rules**. While our approach was based on national guidelines, it may have limited generalizability of findings to **clinical practices where a more conservative approach to glycemic control is practiced**

Conclusions

- Early treatment with metformin was not superior to placebo for the composite primary outcome. Prespecified secondary outcome data support further investigation of metformin in larger clinical trials.