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The role of male foetal sex on maternal and neonatal outcomes in pregnancies complicated by gestational diabetes—secondary analysis of a randomised placebo controlled clinical trial of metformin in gestational diabetes (EMERGE)

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Abstract

Background Male foetal sex is recognised as an independent risk factor for adverse pregnancy outcomes including preterm birth, neonatal care unit admission and lower Apgar scores. Male foetuses appear to increase the risk of maternal gestational diabetes in the mother due to impacts on beta cell function, and in pregnancies impacted by gestational diabetes, male offspring have higher rates of hypoglycaemia, respiratory distress and macrosomia. Metformin exposure in animal models has also demonstrated sex-specific effects with different patterns in adiposity and lipid levels observed between male and female offspring exposed to metformin in utero. The aim of this analysis is to determine whether foetal sex modifies maternal and neonatal outcomes in gestational diabetes, and evaluate the sex-specific response to metformin on insulin usage, fasting glucose at 32 and 38 weeks and foetal size.

Methods We conducted a secondary analysis of the Early Metformin in Gestational Diabetes (EMERGE) randomised controlled trial and analysed neonatal outcomes according to sex and metformin exposure.

Results At randomisation, women carrying a male foetus had a higher plasma glucose at 60 min on oral glucose tolerance testing (9.69 vs. 9.37 mmol/L, $p=0.039$). In exploratory analyses, metformin exposure in male pregnancies was associated with lower fasting glucose at 32 (4.88 vs. 5.01 mmol/L, $p=0.014$) and 38 weeks (4.49 vs. 4.69 mmol/L, $p=0.002$) and reduced insulin use (38% vs. 53%, $p=0.014$), with smaller effects in female pregnancies. Metformin-exposed females had higher rates of birth weight < 2500 g compared to those exposed to placebo (8.3% vs. 1.9%, $p=0.032$), which was not observed in metformin-exposed males. More male offspring had a birth weight > 4000 g compared to female offspring regardless of metformin exposure. However, the sex-by-treatment interaction

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was not significant, so these findings should be regarded as hypothesis-generating. Glucometer data suggested a greater mean glucose reduction in males than females (0.29 mmol/L (95% CI 0.29–0.30) versus 0.21 mmol/L (95% CI 0.20–0.21)).

Conclusions Further follow-up is required to determine whether foetal sex influences long-term effects of metformin in pregnancy.

Keywords Diabetes, Gestational, Male, Metformin, Outcomes

Background

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, conferring increased short- and long-term risks to both mother and offspring [1]. Foetal sex is recognised as an independent risk factor for adverse maternal and neonatal outcomes including pre-eclampsia, preterm delivery, respiratory distress and sepsis [2, 3].

Male sex also impacts GDM with higher rates of GDM observed in those carrying a male foetus. Mothers carrying a male foetus are more likely to require pharmacological treatment for GDM compared to those carrying a female foetus [4]. Male offspring of mothers with GDM have higher rates of macrosomia, caesarean delivery and neonatal care unit compared to female offspring [4]. Long-term follow-up observational studies which have aimed to evaluate the impact of foetal sex on type 2 diabetes mellitus (T2DM) rates have found minimal or statistically insignificant higher rates in women who carried a female foetus (adjusted hazard ratio 1.06, 95% CI 1.01–1.26 and 6.2 vs. 7.1%, $p=0.48$) [5, 6].

Metformin, an oral biguanide used in the treatment of a number of metabolic conditions, including GDM and T2DM, has been associated with adverse childhood cardiometabolic profiles in some studies [7]. The long-term impact of metformin use during pregnancy may result from alteration of epigenetic factors in the placenta, which differ by foetal sex with reduced deoxyribonucleic acid (DNA) methylation, through upregulated adenosine monophosphate (AMP)-activated protein kinase (AMPK), in metformin-exposed male foetuses [8, 9].

To our knowledge, to date, no randomised controlled trial has directly examined whether foetal sex modifies maternal and neonatal responses to metformin.

We therefore performed a secondary, exploratory analysis of the Early Metformin in Gestational Diabetes (EMERGE) randomised controlled trial to evaluate whether foetal sex modifies maternal glycaemic outcomes and neonatal characteristics. Because this analysis was not pre-specified, findings should be regarded as hypothesis-generating.

Methods

Ethical approval was obtained from Galway University Hospital (Clinical Research Ethics Committee of Galway University Hospital (2016–001644-19)).

The trial design protocol and primary outcomes of the EMERGE trial (EudraCT Number: 2016–001644-19; National Clinical Trial 02980276, registered 6/6/2017) have been previously reported [10, 11]. In brief, in the original EMERGE study, a double-blind placebo controlled trial, 535 singleton pregnancies in 510 women with GDM (World Health Organisation criteria) were randomised to either metformin (up to 2500 mg/day) or placebo, in addition to standard care, from diagnosis to delivery. The primary outcome of the original EMERGE trial was a composite of insulin initiation or fasting glucose ≥ 5.1 mmol/L at weeks 32 or 38 gestation, which was not significantly different between groups ($p=0.13$). In the original EMERGE trial, maternal weight gain from randomisation to delivery and time to insulin usage were more favourable in the metformin-exposed group.

Classic analysis

We performed a bivariate analysis (chi-squared tests of association) of the composite outcome and a multivariate analysis to determine the impact of male foetal sex on maternal and neonatal outcomes and to test the sex-by-treatment interaction.

Functional analysis

Glucometer data from individual participants were analysed to determine the impact of treatment on maternal glucose levels. To exclude the effect of insulin, we selected the glucose measurements from randomisation until insulin initiation. For women who did not initiate insulin, we used data from randomisation to delivery.

As each woman's glucometer data were non-linear and measured on a unique time grid, a P-splines smoothing method was applied to the raw glucose data [12]. This approach transforms the noisy glucose measurements into smoothed curves that represent the change in glucose for each woman over a normalised time range

from 0 (i.e. randomisation) to 1 (i.e. delivery or insulin initiation). Smoothing reduces outlier effects by focusing on the underlying trend in glucose over time and normalises each woman's data over a fixed time grid. Functional data analysis was then employed to obtain the functional mean glucose levels for mothers of male and female foetuses, and to apply a functional *t*-test to test the differences between these two functional means for the population of all mothers.

In these analyses, continuous data are presented as mean ± standard deviation or median (IQR) and compared using *t*-tests or Wilcoxon rank-sum tests as appropriate. Categorical data were compared using chi-squared or Fisher exact tests. All analyses were performed using R Statistical Software [13] version 4.4.2.

Results

We include 535 study pregnancies with 289 (54%) male and 236 (46%) female foetuses. A higher proportion of mothers carrying female foetuses were randomised to receive metformin (56% vs. 45%, $p=0.013$) (Table 1).

Foetal sex and maternal outcomes

Baseline maternal characteristics were similar between groups, except those mothers carrying male foetuses had higher 60-min glucose levels on OGTT at randomisation (mean 9.69 mmol/L vs. 9.37 mmol/L, $p=0.039$). At 36 weeks' gestation, HbA1c was higher among women carrying male foetuses (mean 35.0 mmol/mol vs. 33.6 mmol/mol, $p=0.005$), and while this reaches statistical significance, it is likely not clinically significant. At delivery, there was no significant difference in birth weight (mean 3480 g vs. 3412 g, $p=0.134$), although male neonates had higher rates of macrosomia (14.0% vs. 8.1%, $p=0.037$) and larger head circumferences (mean 35.01 cm vs. 34.36 cm, $p<0.001$), regardless of metformin exposure.

Foetal sex, metformin exposure and the primary outcome

Foetal sex was not an independent predictor of the primary composite outcome or any of its components and the sex-by-treatment interaction was not statistically significant ($p=0.692$). Therefore, all subgroup analyses should be interpreted as exploratory. Among women carrying a male foetus, metformin reduced the primary composite outcome (55% vs. 68%, $p=0.024$), insulin use (38% vs. 53%, $p=0.014$) and fasting glucose at 32 and 38 weeks (mean glucose 4.88 mmol/L vs. 5.01 mmol/L, $p=0.021$ and 4.49 mmol/L vs. 4.69 mmol/L, $p=0.002$), respectively (Table 1). Among women carrying a female foetus, metformin usage was associated with reduced maternal weight gain (0.5 vs. 2.3 kg, $p<0.001$), lowered fasting glucose at 38 weeks (4.47 mmol/L vs. 4.63 mmol/L, $p=0.046$) and a higher rate of low birth weight infants (8.3% vs. 1.9%, $p=0.032$) compared to placebo use. Given the non-significant interaction, this subgroup findings should be interpreted as exploratory.

Glucometer data

A total of 435 women provided repeated glucose data (up to 7 readings per day) from GDM diagnosis to delivery/insulin initiation, resulting in 184,410 glucose values (median 413 per pregnancy). At randomisation, mothers carrying a male foetus had a slightly higher mean glucose level (mean 5.74 mmol/L vs. 5.70 mmol/L, $p=0.43$); however, this was not statistically significant. After commencing metformin, mothers carrying a male foetus had greater glucose reductions (0.29 mmol/L (95% CI 0.29–0.30) versus 0.21 mmol/L (95% CI 0.20–0.21)) (Fig. 1).

Discussion

In this secondary analysis of the EMERGE trial, we found that mothers with GDM carrying male foetuses had higher glucose levels at 60 min ($p=0.039$) and that male infants had increased head circumference. Metformin exposure in these mothers was associated with greater reductions in mean glucose levels (glucometer readings), lower insulin requirements and lower fasting glucose levels at gestational weeks 32 and 38. To our knowledge, this is the first study to examine the impact of foetal male sex in the context of an RCT.

The relationship between GDM, GDM risk factors and secondary sex ratio is complex. The Trivers-Willard hypothesis suggests that in times of good physical health and food security, parents are "positively biased towards sons" [14]. A decline in male births following periods of famine in a Chinese population has been previously observed, and this is potentially explained by spontaneously termination of male foetus calorie-restricted environments [15]; however, this phenomenon has not been seen in all epidemiological studies [16].

Other studies, which evaluated body habitus and dietary habits, found that higher waist to hip ratio [17] and higher glucose, free fatty acid and caloric intake result in more male offspring in animal models [18]. In in vitro animal models, male embryos transition to blastocysts more easily when cultured in a high-glucose environment [19]. However, other studies have found a decrease in male births in those with high levels of preconception obesity, so there is still uncertainty regarding the exact relationship between body composition on alternations in secondary sex ratio [20].

When compared to those carrying a female foetus, women carrying male foetuses experience reduced pancreatic beta cell function (after adjustment for

Table 1 Pregnancy characteristics by foetal sex

	Male metformin $N=130$[a]	Male placebo $N=159$[a]	p value[b]	Female metformin $N=132$[a]	Female placebo $N=104$[a]	p value[b]	All male $N=289$[a]	All female $N=236$[a]	p value[b]
Baseline maternal characteristics									
Age (years)	34.7 (5.0)	34.5 (4.4)	0.686	34.1 (4.8)	34.1 (5.0)	0.867	34.6 (4.7)	34.1 (4.9)	0.194
BMI (kg/m^2)	32.1 (6.1)	32.4 (4.8)	0.181	32.1 (5.9)	32.1 (5.9)	0.911	32.3 (5.5)	32.1 (5.9)	0.738
Gestational age (weeks)	25.3 (4.3)	25.5 (4.1)	0.779	25.4 (4.3)	25.5 (4.0)	0.817	25.5 (4.2)	25.4 (4.2)	0.393
Race									
Caucasian (%)	114 (88.0)	121 (76.0)	0.012	112 (85.0)	88 (85.0)	>0.9	235 (81.0)	200 (85.0)	0.321
Other (%)	16 (12.0)	38 (24.0)	0.012	20 (15.0)	16 (15.0)	>0.9	54 (19.0)	36 (15.0)	0.296
Previous history of GDM (%)	31 (24.0)	37 (23.0)	0.922	32 (24.0)	26 (25.0)	0.867	68 (24.0)	58 (25.0)	0.780
Previous history of macrosomic infant (%)	24 (18.0)	25 (16.0)	0.537	32 (24.0)	19 (18.0)	0.268	49 (17.0)	51 (22.0)	0.177
Previous history of hypertension (%)	5 (3.8)	3 (1.9)	0.474	7 (5.3)	1 (1.0)	0.081	8 (2.8)	8 (3.4)	0.680
Previous history of caesarean delivery (%)	34 (26.0)	42 (26.0)	0.961	35 (27.0)	32 (31.0)	0.472	76 (26.0)	67 (28.0)	0.592
OGTT at randomisation									
Fasting plasma glucose (mmol/L)	5.20 (0.46)	5.23 (0.50)	0.706	5.21 (0.45)	5.15 (0.45)	0.148	5.22 (0.48)	5.18 (0.45)	0.676
60-min plasma glucose (mmol/L)	9.49 (1.93)	9.86 (1.94)	0.143	9.26 (1.90)	9.52 (1.78)	0.239	9.69 (1.94)	9.37 (1.85)	0.039
120-min plasma glucose (mmol/L)	7.29 (1.60)	7.21 (1.65)	0.842	7.02 (1.56)	7.03 (1.43)	0.732	7.25 (1.63)	7.03 (1.5)	0.124
Pregnancy outcomes									
Maternal outcomes									
HbA1c at 36 weeks' gestation (mmol/mol)	34.6 (3.3)	35.3 (4.2)	0.427	33.5 (3.7)	33.7 (3.6)	0.792	35.0 (3.9)	33.6 (3.6)	0.005
Fasting glucose at 32 weeks' gestation (mmol/L)	4.88 (0.46)	5.01 (0.49)	0.021	4.90 (0.54)	4.96 (0.50)	0.271	4.95 (0.48)	4.92 (0.52)	0.490
Fasting glucose at 38 weeks' gestation (mmol/L)	4.49 (0.45)	4.69 (0.49)	0.002	4.47 (0.40)	4.63 (0.51)	0.046	4.61 (0.48)	4.54 (0.46)	0.300
Insulin use (%)	49 (38.0)	83 (53.0)	0.014	49 (38.0)	51 (49.0)	0.081	132 (46.0)	100 (43)	0.457
Gestational weight gain (kg)	1.3 (3.3)	1.7 (3.6)	0.296	0.5 (3.3)	2.3 (3.4)	<0.001	1.5 (3.5)	1.3 (3.5)	0.494
Pre-eclampsia (%)	10 (7.7)	16 (10)	0.484	14 (11.0)	7 (6.7)	0.299	26 (9.0)	21 (8.9)	0.969
Pregnancy-induced hypertension (%)	7 (5.4)	12 (7.6)	0.444	9 (6.9)	4 (3.9)	0.324	19 (6.6)	13 (5.6)	0.632

Table 1 (continued)

	Male metformin $N=130$[a]	Male placebo $N=159$[a]	p value[b]	Female metformin $N=132$[a]	Female placebo $N=104$[a]	p value[b]	All male $N=289$[a]	All female $N=236$[a]	p value[b]
Neonatal anthropometrics									
Birth weight (g)	3446 (530)	3508 (547)	0.139	3342 (521)	3500 (449)	0.071	3480 (540)	3412 (496)	0.13
Birth weight < 2500 g (%)	5 (3.8)	7 (4.4)	0.814	11 (8.3)	2 (1.9)	0.032	12 (4.2)	13 (5.5)	0.468
Birth weight > 4000 g (%)	13 (10.0)	27 (17.0)	0.087	7 (5.3)	12 (12.0)	0.080	40 (14)	19 (8.1)	0.037
Head circumference (cm)	35.09 (1.60)	34.96 (1.88)	0.380	34.31 (1.50)	34.42 (1.57)	0.735	35.01 (1.76)	34.36 (1.53)	< 0.001
Crown heel length (cm)	51.34 (3.01)	51.64 (3.42)	0.318	50.7 (3.4)	51.9 (2.9)	0.002	51.5 (3.2)	51.2 (3.2)	0.268
Abdominal circumference (cm)	33.14 (2.34)	33.39 (3.23)	0.097	33.61 (2.47)	33.18 (2.07)	0.194	33.27 (2.85)	33.41 (2.30)	0.746
Arm circumference (cm)	10.91 (1.00)	11.09 (1.23)	0.099	10.99 (1.04)	11.01 (0.97)	0.830	11.01 (1.13)	11.00 (1.00)	0.809
Gestational age at birth (week)	38.99 (1.54)	39.00 (1.74)	0.733	39.16 (1.53)	39.33 (1.22)	0.445	39.00 (1.65)	39.24 (1.40)	0.091
Neonatal outcomes									
Preterm (%)	14 (11.0)	11 (7.0)	0.253	10 (7.6)	6 (5.8)	0.586	25 (8.7)	16 (6.8)	0.436
Caesarean section (%)	59 (45.0)	64 (40.0)	0.380	57 (43.0)	38 (37.0)	0.302	123 (43.0)	95 (40.0)	0.594
Respiratory distress (%)	11 (8.5)	14 (8.8)	> 0.9	13 (9.8)	4 (3.8)	0.077	25 (8.7)	17 (7.2)	0.543
Neonatal hypoglycaemia (%)	17 (13.0)	17 (11.0)	0.531	17 (13.0)	8 (7.7)	0.199	34 (12.0)	25 (11.0)	0.672
Neonatal jaundice (%)	63 (48.0)	89 (57.0)	0.165	65 (50.0)	43 (42.0)	0.235	152 (53.0)	108 (47.0)	0.146
Apgar score < 7 (%)	0 (0)	1 (0.6)	> 0.999	1 (0.8)	0 (0)	> 0.999	1 (0.3)	1 (0.4)	> 0.999
Neonatal ICU admission (%)	20 (15.0)	23 (14.0)	0.827	21 (16.0)	10 (9.6)	0.155	43 (15.0)	31 (13.0)	0.568
Neonatal ICU (days)	6 (11.0)	8 (13.0)	0.691	9 (12.0)	4 (4.0)	0.321	7 (12.0)	7 (10.0)	0.472

BMI, body mass index; *GA*, gestational age; *GDM*, gestational diabetes; *OGTT*, oral glucose tolerance test; *cm*, centimetre; *ICU*, intensive care unit; *HbA1c*, haemoglobin A1c

[a] *n* (%), mean (SD)

[b] Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test

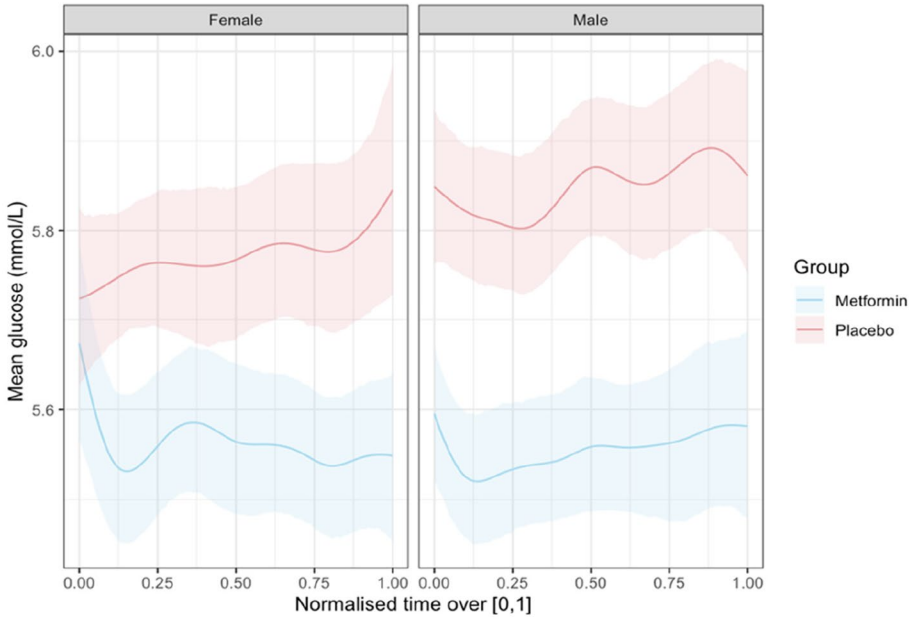

Fig. 1 Mean glucose levels from glucometer data by foetal sex and treatment allocation. Glucose values are smoothed over time from randomisation (0) to delivery or insulin initiation (1). Mothers carrying male foetuses had slightly higher glucose throughout pregnancy and appeared to show greater glucose reduction with metformin compared with those carrying female foetuses (0.29 mmol/L (95% CI 0.29–0.30) vs. 0.21 mmol/L (95% CI 0.20–0.21), respectively). Shaded areas represent 95% confidence intervals. These differences were exploratory; the sex-by-treatment interaction was not statistically significant

body mass index (BMI) and maternal age) [21]. Our findings of reduced fasting glucose level at 38 weeks are consistent with analyses of trial populations, which also reported reduced birthweight and neonatal fat mass in male infants, where the mother was treated for GDM [22]. As the overall sex-by-treatment interaction did not reach statistical significance, these findings need to be interpreted with those limitations. This supports the concept that males benefit more from treatment of GDM because they are hypothesised to be more susceptible to damage from oxidative stress [23].

Based on the findings of this study, the consistent pattern across fasting glucose, insulin use and glucometer profiles strengthens the biological plausibility of sex-specific responses but does not confirm a differential treatment effect. Potential mechanisms include sex-dependent differences in placental function, oxidative stress susceptibility and epigenetic modification [9, 23, 24]. While novel, this study also has a number of limitations. It is a secondary analysis which includes a relatively small sample size and does not offer a direct mechanistic study.

In previously mouse models, female mice carrying a male foetus had greater glucose reductions when exposed to metformin compared to those carrying female foetuses [25]. In this murine study, metformin-exposed female offspring gained more weight, but had a better glucose tolerance than their male counterparts. In similar mouse studies, metformin-exposed female offspring exhibited excess fat and hyperinsulinemia, while males displayed more severe adipocyte dysfunction and hepatic inflammation [26].

In human studies of offspring of mothers with T2DM treated with metformin, male, but not female offspring exposed to metformin had higher BMIs at 6–24 months [27]. A separate follow-up study found that males exposed to metformin had a higher BMI and free fat mass index than those treated with insulin; however, this study was limited by a lack of ethnic diversity and the small number of female offspring included in follow-up [28]. The long-term (3–6 year) follow-up of the offspring from the EMERGE trial is currently underway, and a sex-specific impact of metformin use will be evaluated in the long-term follow-up.

Conclusions

In conclusion, in this secondary, exploratory analysis of the EMERGE trial, male foetal sex was associated with higher maternal glucose levels and an apparent greater reduction in glucose and insulin use with metformin exposure. However, the sex-by-treatment interaction was not significant, and these findings should be regarded as hypothesis-generating. Long-term follow-up of EMERGE offspring will be essential to determine whether foetal

sex influences the enduring effects of metformin in pregnancy.

Abbreviations

GDM	Gestational diabetes mellitus
T2DM	Type 2 diabetes mellitus
DNA	Deoxyribonucleic acid
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate protein kinase
EMERGE	Early Metformin in Gestational Diabetes
BMI	Body mass index

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Nil.

Authors' contributions
CN, RPMcE, DD, AE, AS(2), MOD, POS, DD and FD designed the study. PG, AAI, KE, AS(1) and YZ conducted the statistical analyses. All authors contributed to data interpretation. CN drafted the initial manuscript. All authors provided critical feedback and approved submission. CN and FD are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data availability
Data are available upon request.

Declarations

Ethics approval and consent to participate
Ethical approval was granted by the Clinical Research Ethics Committee of Galway University Hospital (2016–001644-19).

Consent for publication
All participants provided written consent at the time of enrolment and that results would be published in scientific journals.

Competing interests
The authors declare no competing interests.

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