Association between insulin resistance and preeclampsia in obese non-diabetic women receiving metformin

Jyoti Balani[1], Steve Hyer[1], Argyro Syngelaki[2], Ranjit Akolekar[3], Kypros H Nicolaides[2], Antoinette Johnson[4] and Hassan Shehata[4]

Abstract

Objectives: To examine whether the reduced incidence of preeclampsia in non-diabetic obese pregnant women treated with metformin is mediated by changes in insulin resistance.

Methods: This was a secondary analysis of obese pregnant women in a randomised trial (MOP trial). Fasting plasma glucose and insulin were measured in 384 of the 400 women who participated in the MOP trial. Homeostasis model assessment of insulin resistance (HOMA-IR) was compared in the metformin and placebo groups and in those that developed preeclampsia versus those that did not develop preeclampsia.

Results: At 28 weeks, median HOMA-IR was significantly lower in the metformin group. Logistic regression analysis demonstrated that there was a significant contribution in the prediction of preeclampsia from maternal history of chronic hypertension and gestational weight gain, but not HOMA-IR either at randomisation ($p = 0.514$) or at 28 weeks ($p = 0.643$).

Conclusions: Reduced incidence of preeclampsia in non-diabetic obese pregnant women treated with metformin is unlikely to be due to changes in insulin resistance.

Background

Obesity in pregnancy is associated with a number of serious adverse outcomes including gestational diabetes and preeclampsia.[1–3] A recent randomised double-blind placebo-controlled trial of metformin from 12–18 weeks' gestation until delivery in pregnant non-diabetic women with body mass index $>35 \, kg/m^2$ (MOP trial), reported that metformin had no significant effect on birth weight centile, which was the primary outcome, nor did it reduce the risk of GDM.[4] However, in the metformin group, compared to placebo, there was a lower median gestational weight gain (4.6 kg, interquartile range (IQR) 1.3–7.2 vs. 6.3 kg, IQR 2.9–9.2, $p < 0.0001$) and incidence of preeclampsia (3.0% vs. 11.3%; odds ratio (OR) 0.24, 95% confidence interval (CI) 0.10–0.61; $p = 0.001$).[4] This is a secondary analysis of the MOP trial[4] to investigate whether the reduced incidence of preeclampsia in non-diabetic obese pregnant women treated with metformin is mediated by changes in insulin resistance.

Materials and methods

Individuals included in this study were participants of the MOP trial that has been previously reported.[4] In this trial, 400 women were randomised in a 1:1 ratio to either active treatment with metformin or to placebo. In 384 participants, written informed consent was obtained for fasting blood samples at randomisation at 15 (12–18) weeks' gestation and again at 28 (25–33) weeks. Ethical Approval was obtained from the London-Surrey Borders Research Ethics committee (REC no 08/H0806/80) (EudraCT no. 2008-005892-83).

The plasma was separated and frozen at $-20°C$. Samples were batched and analysed together to avoid inter-assay variation. Plasma glucose reagents were provided by Siemens Healthcare Diagnostics Ltd, Surrey, UK; the lower limit of detection of the assay was 0.4 mmol/L and the intra-assay and inter-assay coefficients of variation at a concentration of 4.4 mmol/L were 0.6% and 1.6%, respectively. Plasma insulin was measured by a two-site sandwich immunoassay

(reagent supplied by Siemens Healthcare Diagnostics Ltd, Surrey, UK); the lower limit of detection of the assay was 0.5 mIU/L and the intra-assay and inter-assay coefficients of variation at a concentration at a concentration of 45.72 mIU/L were 3.2% and 2.6%, respectively. All samples were analysed in duplicates and those with a coefficient of variation exceeding 10% were re-analysed. None of the samples in this study were previously thawed and refrozen. Insulin resistance was assessed by the homeostatic model (HOMA-IR) score, which correlates well with direct evaluation using a glucose clamp[5] and has been validated in pregnancy.[6] HOMA-IR was calculated by multiplying fasting insulin in mIU/L with fasting glucose in mmol/L divided by 22.5.

Statistical analysis

The distribution of glucose, insulin and HOMA-IR were assessed for normality using histograms and probability plots. Logarithmic transformation was necessary to achieve Gaussian normality. Mann–Whitney U test was used to compare the median $\log_{10}$ values of glucose, insulin and

[1]Department of Endocrinology, Epsom and St Helier University Hospitals NHS Trust, Surrey, UK
[2]Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital, London, UK
[3]Department of Fetal Medicine, Medway Maritime Hospital, Kent, UK
[4]Department of Maternal Medicine, Epsom and St Helier University Hospitals NHS Trust, Surrey, UK

Corresponding author:
Jyoti Balani, Department of Endocrinology, Doreen Kouba Diabetes Centre Epsom and St Helier Hospital University Hospitals NHS Trust, Wrythe Lane, Carshalton, Surrey, SM5 1AA, UK.
Email: jyoti.balani@nhs.net

Table 1. Baseline maternal characteristics in the preeclampsia and non-preeclampsia groups.

Characteristics	Metformin n = 196	Placebo n = 188	p Value	Preeclampsia n = 22	No preeclampsia n = 362	p Value
Maternal age in years, median (IQR)	32.8 (27.3–36.1)	30.8 (26.6–34.5)	0.036	32.5 (26.0–36.5)	31.6 (27.2–35.4)	0.993
Maternal weight in kg, median (IQR)	104.8 (95.7–116.3)	105.3 (97.2–114.4)	0.719	109.7 (103.9–113.3)	104.8 (96.0–116.0)	0.134
Maternal height in cm, median (IQR)	165 (159.8–168)	165 (160–169)	0.453	165 (159–172)	165 (160–168)	0.355
Body mass index, median (IQR)	38.7 (36.5–41.5)	38.4 (36.3–41.9)	0.653	39.7 (37.2–43.4)	38.4 (36.3–42.0)	0.314
Gestational age at randomisation in weeks, median (IQR)	15.1 (13.7–16.9)	14.7 (13.6–17.1)	0.429	14.5 (13.4–18.3)	15.3 (13.9–17.5)	0.410
Gestational age at second sampling in weeks, median (IQR)	28.1 (27.7–28.6)	28.1 (27.7–28.7)	0.156	28.1 (27.9–28.8)	28.1 (27.7–28.6)	0.467
Racial origin			0.621			0.476
Caucasian, n (%)	139 (70.9)	123 (65.4)		13 (59.1)	248 (68.5)	
Afro-Caribbean, n (%)	47 (24.0)	51 (27.1)		7 (31.8)	91 (25.3)	
Asian, n (%)	8 (4.1)	12 (6.4)		2 (9.1)	18 (5.0)	
Mixed, n (%)	2 (1.0)	2 (1.1)		0	5 (1.4)	
Medical history						
Chronic hypertension, n (%)	11 (5.6)	17 (9.0)	0.196	7 (31.8)	21 (5.8)	<0.001
Cigarette smokers, n (%)	14 (7.1)	20 (10.6)	0.228	2 (9.1)	32 (8.8)	1.000
Conception			0.784			0.415
Spontaneous, n (%)	191 (97.5)	184 (97.9)		21 (95.5)	354 (97.8)	
Assisted reproduction, n (%)	5 (2.6)	4 (2.1)		1 (4.5)	8 (2.2)	
Parity						
Nulliparous, n (%)	55 (28.1)	65 (34.6)	0.169	12 (54.5)	108 (29.8)	0.030
Parous with previous preeclampsia, n (%)	14 (7.1)	11 (5.9)	0.608	3 (13.6)	22 (6.1)	0.165

IQR = interquartile range. Comparisons between outcome groups were performed by Chi-square test for categorical variables and Mann–Whitney test for continues variables.

HOMA-IR between the metformin and placebo groups and between the preeclampsia and non-preeclampsia groups. Multivariable logistic regression analysis was used to determine whether nulliparity, chronic hypertension, weight at randomisation, gestational weight gain and glucose, insulin and HOMA-IR at 15 and 28 weeks provided significant independent contribution in prediction of preeclampsia. The statistical software IBM SPSS Statistics version 22.0 with adjustment for unequal allocated groups was used for data analyses.

Results

Of the 384 patients who participated in this study, 196 women received metformin and 188 women received placebo. The maternal characteristics and history of the preeclampsia and non-preeclampsia groups are presented in Table 1. In the women who developed preeclampsia, compared to the non-preeclampsia group, there was a higher incidence of nulliparity and chronic hypertension.

Comparison between the metformin and placebo groups demonstrated that at randomisation there were no significant differences in fasting plasma glucose, fasting plasma insulin and HOMA-IR, but at 28 weeks' gestation, in the metformin group fasting plasma insulin and HOMA-IR were significantly reduced (Table 2). Comparison between the preeclampsia and non-preeclampsia groups demonstrated no significant differences in fasting plasma glucose, fasting plasma insulin or HOMA-IR, either at randomisation or at 28 weeks' gestation (Table 2). The median 2-hour postprandial glucose values were similar at randomisation (5.2 vs. 5.3 mmol/L; p:NS) and at 28 weeks gestation (5.3 vs. 5.5; p:NS).

Logistic regression analysis demonstrated that in the prediction of preeclampsia there was a significant contribution from chronic hypertension (OR 2.7; 95% CI 4.6–45.0, $p < 0.001$) and gestational weight gain (OR 1.14; 95% CI 1.06–1.23, $p = 0.001$), but not from weight at randomisation ($p = 0.517$), parity ($p = 0.061$), glucose, insulin or HOMA either at randomisation ($p = 0.504$, $p = 0.492$, $p = 0.514$, respectively) or at 28 weeks' gestation ($p = 0.397$, $p = 0.924$, $p = 0.643$, respectively).

Discussion

The findings of this study suggest that the reduced incidence of preeclampsia in non-diabetic obese pregnant women treated with metformin is not due to changes in insulin resistance. There were no significant differences in fasting plasma glucose, fasting plasma insulin or HOMA-IR between the preeclampsia and non-preeclampsia groups either at randomisation or at 28 weeks' gestation. Furthermore, neither plasma glucose nor plasma insulin or HOMA-IR either at randomisation or at 28 weeks provided a significant contribution in the prediction of preeclampsia.

Some studies reported that in women who develop preeclampsia maternal HOMA-IR is increased and this increase precedes the clinical onset of the disease and it may be apparent from the first trimester of pregnancy.[7–12] However, several other studies found no significant differences in HOMA-IR between preeclamptic and non-preeclamptic groups in the first, second or third trimesters of pregnancy or at the time of delivery.[13–19]

Preeclampsia has a complex pathophysiology and the primary cause is thought to be impaired placentation leading to placental hypoxia and

Table 2. Comparison between outcome groups for biomarkers of insulin resistance at 15 and 28 weeks' gestation.

Marker	Metformin $n = 196$	Placebo $n = 188$	p Value	Preeclampsia $n = 22$	No-preeclampsia $n = 362$	p Value
At 15 weeks' gestation (enrolment)						
Fasting glucose mmol/L, Median (IQR)	4.4 (4.2–4.6)	4.5 (4.2–4.8)	0.052	4.5 (4.2–4.8)	4.4 (4.2–4.7)	0.331
Fasting insulin mIU/L Median (IQR)	18.4 (12.9–27.7)	18.1 (12.3–26.8)	0.584	21.0 (15.9–29.7)	18.1 (12.3–27.1)	0.170
HOMA-IR Median (IQR)	3.8 (2.4–5.4)	3.6 (2.4–5.5)	0.908	4.2 (3.2–6.0)	3.6 (2.3–5.4)	0.110
At 28 weeks' gestation						
Fasting glucose mmol/L Median (IQR)	4.4 (4.1–4.8)	4.4 (4.1–4.8)	0.804	4.5 (4.0–4.9)	4.4 (4.1–4.8)	0.990
Fasting insulin mIU/L Median (IQR)	19.7 (14.0–31.0)	22.9 (15.2–33.6)*	0.046	24.3 (15.3–39.7)	21.5 (14.6–32.0)	0.220
HOMA-IR Median (IQR)	3.9 (2.6–5.7)	4.6 (3.0–6.8)**	0.005	4.8 (3.4–8.5)	4.2 (2.7–6.0)	0.115

IQR = interquartile range. Comparison between groups was performed by Mann–Whitney *U* test.
*$p < 0.05$; **$p < 0.01$.

oxidative stress with consequent release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG), into the maternal circulation, which in turn lead to endothelial dysfunction and multisystem organ injury.[20–25] A recent *in vivo* study demonstrated that metformin reduces the release of sFlt-1 and sENG from placental and endothelial cells and the release of sFlt-1 from placental villous explants from women with severe preeclampsia.[26]

Our study demonstrated as expected, that metformin treatment compared to placebo, was associated with a reduction in plasma insulin and HOMA-IR at 28 weeks' gestation. There is extensive evidence to support this effect of metformin in pregnant and non-pregnant individuals.[27,28] A large RCT on 2155 non-diabetic adults with elevated fasting and post-load plasma glucose concentrations reported that use of metformin, compared to placebo, was associated with a 31% lower incidence of type 2 diabetes mellitus after an average follow up of 2.5 years.[29] During pregnancy, metformin has been widely used in women with polycystic ovarian syndrome and several studies have demonstrated its association with improved insulin sensitivity.[28,30–32] Normal pregnancy is associated with an incremental rise of fasting insulin at 28 weeks of gestation and this increase is attenuated by metformin. One study showed that metformin decreases HOMA-IR score by 4.4% at 28 weeks of gestation.[28] A recent randomised controlled trial (EMPOWaR) in non-diabetic women with BMI $>30\,kg/m^2$ found no significant differences between the metformin and placebo groups in either the primary outcome, which was median birth weight, or in any of the secondary outcomes, including gestational weight gain and rate of preeclampsia.[33] The authors reported significantly lower HOMA-IR scores and fasting glucose in the metformin group at 28 weeks gestation but not at 36 weeks. Nevertheless, we and the authors of the EMPOWaR trial failed to demonstrate a reduction in the incidence of GDM in the metformin group.[33] Metformin was discontinued for a week prior to OGTT in our study but not in the EMPOWaR study. There was no significant difference in the rate of preeclampsia in women receiving placebo (22 (10%)) versus those treated with metformin (19 (8%)) in the EMPOWaR trial. However, failure of the EMPOWaR trial to demonstrate, as in our study, that the use of metformin reduces the rate of preeclampsia may be the consequence of poor adherence to the study regimen, wherein, women took 2.5 g of metformin for only 38% of the duration of the trial.[33] The attenuated rise in HOMA-IR induced by metformin at 28 weeks of gestation seen in the MOP trial was also observed in the EMPOWaR trial, although by 36 weeks, differences in HOMA-IR in that trial had become non-significant. The strength of this study is its randomised controlled design. A major limitation of the study is that the primary outcome of the MOP trial was birthweight and the study was not adequately powered for the secondary outcomes such as preeclampsia.

Conclusions

Whilst metformin significantly reduced fasting insulin and HOMA-IR at 28 weeks, we observed no statistical differences in plasma glucose, plasma Insulin or HOMA-IR comparing women in the preeclampsia and non-preeclampsia groups. We conclude that the finding of a reduced incidence of preeclampsia in obese non-diabetic pregnant women treated with metformin is unlikely to be mediated via changes in insulin resistance. Further studies will be necessary to investigate the potential beneficial effects of metformin in obese non-diabetic pregnant women.

Ethical approval

Ethical approval was obtained from the London-Surrey Borders Research Ethics committee (REC no 08/H0806/80) (EudraCT no. 2008-005892-83). Informed written consent was obtained from all the participants.

Guarantor

Contributorship

Note

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