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SHORT COMMUNICATION

The sex of the foetus affects maternal blood glucose concentrations in overweight and obese pregnant women

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ABSTRACT

There is increasing evidence that the sex of the foetus may alter the maternal metabolic milieu during pregnancy. Following a randomized controlled trial of exercise in overweight and obese pregnant women, we assessed whether the sex of the foetus was associated with changes in maternal metabolism. Data were analysed on 74 randomized participants who completed the trial, including 38 mothers carrying males and 36 mothers carrying females. At 19 weeks of gestation, mothers carrying boys had higher blood glucose concentrations than those carrying girls (5.4 vs 4.9 mmol/l; $p = .046$). At 36 weeks of gestation, differences were more marked, with blood glucose concentrations 15% higher in mothers carrying females (5.7 vs 5.0 mmol/l; $p = .004$). In addition, mothers carrying girls had higher concentrations of hs-CRP across pregnancy (5.0 vs 3.6 mg/l; $p = .029$). Our findings provide further evidence that the sex of the foetus appears to influence maternal metabolism.

KEYWORDS

Maternal; metabolism; cord blood; pregnancy; obesity; foetus

Introduction

Pregnancy is a critical time period, when numerous factors may alter maternal and/or foetal metabolism (e.g. Godfrey and Barker 2000; King 2006). There is increasing evidence that the short- and long-term effects of intrauterine stressors on the offspring vary according to sex (Gabory et al. 2013). However, there is also increasing evidence that the sex of the foetus may in turn affect the maternal environment, and a number of recent studies have shown that foetal sex may alter the maternal metabolic milieu during pregnancy (Sheiner et al. 2004; Xiao et al. 2014; Jaskolka et al. 2015; Retnakaran et al. 2015; Retnakaran and Shah 2015; Walsh et al., 2015). Thus, following a randomised controlled trial of exercise in overweight and obese pregnant women (Seneviratne et al. 2016), we aimed to assess whether foetal sex was associated with changes in maternal metabolism.

Materials and methods

The IMPROVE (Improving Maternal and Progeny Obesity via Exercise) trial was a parallel two-arm randomised controlled trial of exercise in overweight and obese pregnant women in New Zealand (Seneviratne et al. 2016). Ethics approval was obtained from the Health and Disability Ethics Committee. Participants were non-smoking pregnant women aged 18–40 years with a BMI $\geq$25 kg/m^2 and a singleton pregnancy $<$20 weeks of gestation. Exclusion criteria included multiple pregnancy and pre-existing contraindications to antenatal exercise.

Assessments were performed at baseline (19 weeks of gestation) and post-intervention (36 weeks). Venous blood was collected in a non-fasting resting state, at an average of 2.8 and 2.6 h post meal at 19 and 36 weeks of gestation, respectively. Cord blood was collected at birth by delivery staff. Prespecified metabolic markers assessed included glucose, leptin, interleukin-6, tumour necrosis factor alpha and high-sensitivity C-reactive protein (hs-CRP). Maternal chronic glycaemia was assessed by glycated haemoglobin (HbA1c), while maternal sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein 1 (IGFBP-1) were used as surrogate measures of insulin resistance.

Simple two-sample tests were used to compare demographic characteristics between mothers of male and female foetuses. Associations between foetal sex and study outcomes at 19 and 36 weeks of gestation were assessed using generalised linear regression models, adjusting for maternal parity, age and BMI (as well as trial allocation group for the later period). Similar models were used to examine possible effects on cord blood parameters. Maternal data were also examined across pregnancy using repeated measures analysis. Based on our baseline data, our sample size was powered to detect differences between groups in maternal glucose, HbA1c and SHBG levels of 0.61 mmol/l, 0.17% and 74 mmol/l, respectively (with $\alpha = .05$ and 80% power); noting however, that the statistical power was increased by adjustment for important confounders.

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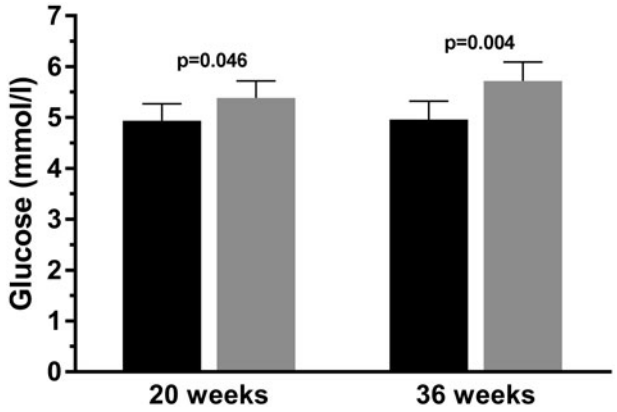

Figure 1. Differences in blood glucose concentrations in mothers of male (black; $n = 38$) and female (grey; $n = 36$) foetuses at 19 and 36 weeks of gestation. Data are means and 95% confidence intervals, adjusted for maternal age, BMI and parity (as well as trial allocation group for the later period).

Results

Data were analysed on the 74 randomised participants who completed the trial (Seneviratne et al. 2016). Mothers carrying male ($n = 38$) and female ($n = 36$) foetuses had similar demographic characteristics, with no significant differences in age, BMI, ethnic composition and dietary intake (data not shown), or rates of gestational diabetes (8% per group).

At 19 weeks of gestation, mothers carrying female foetuses had higher blood glucose concentrations than those carrying males (5.4 vs 4.9 mmol/l; $p = .046$) (Figure 1). At 36 weeks of gestation, differences were more marked, with blood glucose concentrations being 15% higher in mothers of female foetuses (5.7 vs 5.0 mmol/l; $p = .004$) (Figure 1). Repeated measures analysis confirmed this gender difference across pregnancy (5.6 vs 4.9 mmol/l; $p = .002$). Interestingly, maternal glucose concentrations at 19 weeks of gestation were positively correlated with offspring birth weight SDS ($r = .25$; $p = .035$) across the whole cohort, but not at 36 weeks of gestation. This association persisted in multivariable models adjusting for confounders ($\beta = .287$; $p = .024$).

There were no differences in maternal concentrations of SHBG, IGFBP-1, HbA1c, but mothers carrying females had higher concentrations of hs-CRP across pregnancy (5.0 (95%CI 4.0–6.2) vs 3.6 (95%CI 2.9–4.5) mg/l; $p = .029$). Note that the time elapsed between the last meal and the blood test was similar between sexes at baseline ($p = .54$) and post-intervention ($p = .90$). Further, results were largely unaffected by the addition of this time parameter into multivariable models (data not shown). There were no differences in cord blood parameters according to foetal sex (data not shown).

Discussion

This study showed that among overweight or obese mothers, those carrying female foetuses had higher blood concentrations of glucose (particularly in late gestation) and an inflammatory marker (hs-CRP). However, we did not observe differences in markers of insulin resistance.

These data add to the current conflicting evidence. Previously, it has been shown that women carrying male foetuses were more insulin resistant (Walsh et al. 2015) and more likely to develop gestational diabetes (Sheiner et al. 2004; Jaskolka et al. 2015; Retnakaran et al. 2015; Retnakaran and Shah 2015). In contrast, Xiao et al. recently showed greater insulin resistance in mothers carrying a female foetus (Xiao et al. 2014), while (Retnakaran and Shah 2016) observed that, among women who had gestational diabetes, those carrying a girl had a higher risk of developing type 2 diabetes later on.

Our findings provide further evidence that the sex of the foetus appears to influence maternal metabolism, but we found no differences in cord blood metabolic parameters. Although the effects of foetal sex on the long-term health of the mother are still unknown, these are likely to occur via the described association with maternal glycaemia and gestational diabetes risk, since the latter is associated with at least a sevenfold increased risk of developing type 2 diabetes mellitus in the future (Bellamy et al. 2009). Nonetheless, the mechanisms underpinning the observed effects of foetal sex on maternal metabolism are unclear, but they may be associated with alterations on maternal β-cell function during pregnancy (Retnakaran et al. 2015). As the reasons for the conflicting data in the literature are also unknown, further investigation in this area is required.

Disclosure statement

The authors have no financial or non-financial interests to declare that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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