

MATERNAL RISK FACTORS & CHILDHOOD INSULIN RESISTANCE

There is an urgent need to understand maternal factors contributing to childhood diabetes because of the rising incidence of the condition. A new study looks at the independent contributions of pre-pregnancy maternal body size, pregnancy weight gain and gestational diabetes to childhood insulin resistance. The findings suggest the existence of pathways influencing glucose homeostasis during very early development

Both Type 2 diabetes and insulin resistance are becoming increasingly common among adolescents and children. An unhealthy lifestyle, with too much 'junk' food and not enough exercise, is often blamed. However, these disorders may also be transmitted through the generations by a combination of genetic and environmental pathways, including exposures occurring *in utero*.

Maternal diabetes, whether pre-existing or gestational, is known to have an adverse effect on foetal development and insulin-mediated glucose homeostasis in the woman's offspring. Maternal overweight or obesity is also risky in the periconceptual phase, while weight gain during pregnancy may also play a role in increasing the risk of Type 2 diabetes and related disorders during childhood.

Previous research has shown that adolescents with Type 2 diabetes were more likely to have been exposed to both gestational diabetes and maternal obesity. Meanwhile, insulin resistance during childhood is a good marker for adult Type 2 diabetes. Three studies have shown that there is a link between maternal body size and childhood insulin resistance where the woman had normal

glucose tolerance. However, another study showed no link between gestational diabetes and insulin resistance in the child at ages 8 and 11 years. Thus, the literature to date on maternal factors and childhood diabetes or insulin resistance is both small and inconsistent.

Previously, the child's body size has been considered a confounding factor in these studies. However, suppose that maternal diabetes or overweight increased the risk of childhood diabetes via hypothalamic pathways. Then the child's body size becomes a mediator, rather than a confounder.

To help clarify the role maternal factors play in dysfunctional glucose metabolism in childhood, Vivienne Moore and her team at the University of Adelaide have published a significant new study. This looks at the



independent contribution that three antenatal factors – maternal body size, gestational diabetes and weight gain during pregnancy – make to insulin resistance among a group of 9- to 10-year-old children.

A secondary aim of the study was to look at the potential mediating role of the child's body size in any associations thus observed.

Study participants

The current study is based upon the analysis of a subgroup of 163 children aged 9 to 10 years drawn from the Generation 1 study. This is a prospective longitudinal study of women and their children. Healthy Caucasian women were recruited before 16 weeks of pregnancy from four antenatal clinics in Adelaide, South Australia.

Altogether, 557 women completed the pregnancy stage of the study and gave birth. Data were collected at 16 and 32 weeks gestation, at birth and on eight subsequent occasions, the most recent of which was when the children had reached the age of 9 to 10 years. Then 443 women and their children completed questionnaires and anthropometric measurements and 163 of the children gave blood samples.

Data collection

The women completed structured interviews in early and late pregnancy, with height being measured on the first occasion and weight on both. They were also asked about pre-pregnancy weight. Finally, cases of gestational diabetes were recorded.

Babies were measured and weighed at birth. Then, at the 9 to 10 year follow-up, the child's weight and height were measured. In the subgroup that had given blood samples, blood glucose and insulin levels were measured and insulin resistance identified from this data using the homeostasis model assessment [HOMA-IR] formula. Both maternal and child data were then subject to appropriate statistical analysis.

Maternal body weight

The proportions of women found to be overweight or obese at the start of their pregnancy were 23 per cent and 17 per

Maternal factors will decide influence whether a baby develops insulin resistance later on



cent respectively. The average estimated gestational weight gain was 14kg, with 15.3 per cent of the women gaining less weight than recommended, and 45.4 per cent gaining more. Nine women (6 per cent) developed gestational diabetes, of whom five were overweight or obese. For the 9- to 10-year-old children, median fasting glucose was 4.9mmol/l, fasting insulin was 10.7 μ U/ml and HOMA-IR score was 2.3. Children born to mothers with gestational diabetes had significantly higher HOMA-IR scores compared with those whose mothers did not have the condition. Looking at pre-pregnancy weight and childhood insulin resistance showed that in the normal to overweight maternal body mass index (BMI) there were progressive, broadly similar increases in child insulin resistance. In the obese range, the link between pre-pregnancy weight and child insulin resistance was more complex. The relationship between pre-pregnancy weight and child HOMA-IR was independent of gestational diabetes. Finally, weight gain in pregnancy was

not associated with child HOMA-IR. The analysis took account of several potential confounders.

Gestational diabetes

Gestational diabetes was linked to child insulin resistance and this did not seem to be due to high birthweight or current weight of exposed children. This is consistent with other studies. These findings strengthen the case for more diligent diagnosis and management of even mild cases of gestational diabetes, to spare the child the adverse impact upon glucose homeostasis (see also Fact File, this issue).

The complexity of the relationship between maternal pre-pregnancy weight and child insulin resistance, with a discontinuity at BMI around 30, suggests a biological 'ceiling' on this influence, for reasons which are not fully understood.

The finding that this relationship is independent of gestational diabetes is echoed in earlier studies on both African Caribbean and Indian children. However, in these other studies, the

association was found to be mediated by the child's body size, which was not the case in the current study.

Maternal-child glucose regulation pathways

The authors note that their findings could reflect a common genotype or a common postnatal environment among their study population. However, they could also be explained by developmental programming, including epigenetic and other changes that may occur in the intrauterine environment. These changes have been shown to affect development of the foetus from before implantation. Maternal body size before pregnancy has an important impact on the intrauterine environment, increasing the exposure of oocyte, embryo and then foetus to higher maternal glucose and potentially activating inflammatory

pathways. Previous research has suggested various mechanisms, including altered regulation of energy balance via the hypothalamus. For instance, animal experiments have shown that maternal hyperglycaemia can alter hypothalamic control of appetite and body weight in offspring, as well as development of their adipocytes and fat mass. The authors believe their findings support the existence of other pathways where exposure to high maternal glucose during very early development could directly impair the action of insulin in the foetus.

The way forward

It can be argued from this study that attending to diet and glucose control in women of childbearing age could be as important as treating gestational

diabetes for the future health of their babies. While recommended preconception counselling does include weight management, uptake of these services is currently limited and, also, many pregnancies are unplanned. Thus, it may be worthwhile making healthy weight a talking point in all primary healthcare encounters with women of childbearing age.

i This is a digested version of **Maffei O, Whitrow MJ, Davies MJ et al (2015). Maternal body size prior to pregnancy, gestational diabetes and weight gain: associations with insulin resistance in children at 9–10 years. *Diabetic Medicine* 32 (2); 174-180. To download the article, go to: <http://onlinelibrary.wiley.com/doi/10.1111/dme.12637/pdf>**

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