Response of unborn children to glucose associated with mother's insulin sensitivity

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A study published in *Diabetologia* (the journal of the European Association for the Study of Diabetes) is the first to provide direct evidence that fetal brain response to a dose of sugar given orally to its mother is associated with the mother's insulin sensitivity. This may indicate that the risk of subsequent obesity and diabetes may be pre-programmed in the womb. The study is by Dr Hubert Preissl and Dr Andreas Fritsche, University of Tübingen, Germany and German Center for Diabetes Research (DZD), Neuherberg, Germany, and colleagues.

Diabetes or obesity in the mother are already known to influence fetal development and subsequent development after birth. Children of obese or diabetic mothers have an increased risk for type 2 diabetes and obesity in adulthood, independent of their genetic background. Further to this, the prevalence of obesity and type 2 diabetes mellitus is rising worldwide and the percentage of young people affected is increasing. The reasons for these changes are unclear, although environmental and epigenetic mechanisms (where environmental factors affect genetics) are likely to be involved. A major epigenetic mechanism is the so-called fetal programming system, whereby the mother's exposure to environmental factors can affect programming of the genes in her unborn child.

In this new study, Preissl and colleagues aimed to show that the metabolism of a pregnant woman, following a meal, influences fetal brain activity. A total of 13 healthy pregnant women underwent an oral glucose tolerance test (75 g of glucose delivered orally, a standard

method for determining insulin sensitivity). Insulin sensitivity was determined by glucose and insulin measurements at 0, 60 and 120 min. At each time point, the response of the fetus was examined by recording fetal brain responses elicited by sounds with a magnetoencephalographic device.

The researchers found that after 60 minutes, women who were more insulin resistant had fetuses that reacted more slowly to the sound test. When divided into two groups based on insulin sensitivity, the insulin-resistant mothers had fetuses that reacted to the sound at an average of 283 milliseconds, compared with 178 ms for the insulin-sensitive group.

They suggest that the findings support a hypothesis first made almost 50 years ago (1967) by scientist Jørgen Pedersen. The authors say: "It is possible that insulin-resistant mothers have higher glucose levels accompanied by increased insulin levels after a meal. As glucose passes the placenta, these increased glucose levels induce excess insulin (hyperinsulinaemeia) in the fetus. Therefore, high insulin levels in the mother may correspond to high insulin levels in the fetus."

They add: "It is possible that high insulin levels are a prerequisite for appropriate brain maturation. However, chronic hyperinsulinaemia, which is present in insulin-resistant mothers and corresponds to high insulin levels in the fetus, might induce insulin resistance in the fetal brain."

The authors also discuss other possible reasons for the difference in audio response times, including that the insulin resistance of the mother may be associated with limited insulin transport into the fetal brain; alternatively, the insulin resistance of the mother may be associated with a variety of other hormonal and metabolic fuel effects that control the response of the fetal brain.

The consequences for the unborn child are also spelt out, with the authors saying: "The insulin resistance of the fetal brain may be interpreted as metabolic imprinting of insulin resistance with important consequences for later life. The consequent effect of hyperinsulinaemia on fetal development has already been shown. Compared with newborns of non-diabetic women, children of diabetic mothers with poorly controlled glycaemia show neurophysiological impairment and have a higher risk for metabolic syndrome, obesity and type 2 diabetes mellitus in later life."

The authors conclude: "Lower maternal insulin sensitivity is associated with slower fetal brain responses. These findings provide the first evidence of a direct effect of maternal metabolism on fetal brain activity and suggest that central insulin resistance may be programmed during fetal development."

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