Authors' reply re: Maternal lipids are associated with newborn adiposity independent of GDM status, obesity and insulin resistance: a prospective observational cohort study. (Response to BJOG-20-0319)

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May 5, 2020

Letter to the Editor, BJOG Exchange

Authors' reply re: Maternal lipids are associated with newborn adiposity independent of GDM status, obesity and insulin resistance: a prospective observational cohort study

Sir,

We thank Muggleton et al) Muggleton, 2020, Re: Maternal Lipids are associated with newborn adiposity independent of GDM status', obesity and insulin resistance: a prospective observational cohort study([1] for their interest in our paper.

We concur with Muggleton et al[1] that our study[2] reveals only an association (as indicated by the title of our paper) between maternal hypertriglyceridemia and neonatal anthropometrics and cannot provide proof of causality[2]. Studies in Caucasian populations have revealed a similar association between maternal triglyceride and newborn adiposity both in mothers with Gestational Diabetes Mellitus(GDM) and in Normal Glucose Tolerance mothers[2]. Hence, while it is true that a high carbohydrate diet can result in hypertriglyceridemia and may have partially contributed to elevated triglycerides in our Malaysian mothers, given similar associations found in Western populations we do not believe this to be solely modulated by a uniquely 'Malaysian diet' but rather a consequence of obesity and associated maternal insulin resistance. We did not however collect data on dietary intake and therefore cannot objectively confirm the role of a high-carbohydrate diet in our sample population.

We do not however think that based on present published literature that there is sufficient evidence to definitively support the hypothesis that high carbohydrate induced maternal insulin secretion directly increases neonatal adiposity. It is well-established that endogenous fetal hyperinsulinemia as reflected by elevated cord-blood c-peptide correlates strongly with fetal overgrowth and fetal fat accretion secondary to increased fetal triglyceride synthesis/deposition and stimulation of white adipocyte growth.[3] By contrast, it has not however been conclusively established that maternal hyperinsulinemia plays a direct causative role in fetal

overgrowth. The presence of insulin receptors on the placenta has led some to hypothesize that maternal insulin affects transplacental nutrient transport in women with GDM[4]. Although maternal insulin itself does not cross the placenta, it has been postulated that placental insulin resistance results in abnormal insulin signaling pathways in the placenta thus perhaps influencing placental metabolism. Exogenous insulin treatment of GDM mothers however has been found to be beneficial. Langer et al have demonstrated macrosomia rates were lower in insulin-treated GDM mothers compared with diet-treated controls despite equivalent glycemic control, indicating that exogenous insulin has no adverse impact on the fetus at least in the short term and rather results in improved neonatal outcomes[5]. It is also important to note that high levels of maternal insulin are a consequence of the maternal insulin resistance in adipose tissue/skeletal muscle, which plays a significant role in the pathophysiology of GDM. Therefore increased circulating maternal insulin *per se* which has been associated with increased fetal adiposity[4], may not necessarily be directly causative. All these variables are part of a complex inter-connected metabolic web with feedback loops that make it difficult to pinpoint one particular element as the definitive prime mover or underlying cause.

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(On behalf of the authors)

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