

## The causes and effects of fetal macrosomia in mothers with type 1 diabetes

The mechanisms and physiology of in utero fetal nutrition are not understood, and the proportions of carbohydrate, fat, and protein contributing to fetal energy uptake are unknown. Lipids are energy rich and potentially a valuable source of energy for the fetus. Little intact triglyceride crosses the placenta but non-esterified fatty acids (NEFAs) do cross easily. However, the plasma concentration of maternal NEFAs is too low to sustain the total energy supply to the fetus and, therefore, monosaccharides have been assumed to be the major energy source for the growing fetus.

There are considerable species variations in placental fatty acid transfer. In general, the fewer the numbers of cell layers contributing to the placental barrier the higher the net flux. Most experimental biology of materno-fetal energy transport has been performed in species with non-haemochorial placentation. Human placentation is haemochorial—maternal blood is in direct contact with a thin layer of fetal cells. The guinea pig also has a haemochorial placenta and is able to hydrolyse triglyceride, producing NEFAs that cross to the fetus.<sup>1</sup>

Human experimentation is more difficult, but dysnutrition may give insights into normal physiology. In this issue Merzouk *et al* describe mothers with type 1 diabetes mellitus who were delivered of “macrosomic” neonates with higher glucose concentrations and higher triglyceride concentrations than mothers with type 1 diabetes mellitus and appropriate for gestational age neonates.<sup>2</sup> The mothers’ dyslipidaemia might be more than just an association with the hyperglycaemia, in relation to the fetal macrosomia. Placental lipase could hydrolyse triglyceride and the NEFAs liberated might cross to the fetus. Fetal hyperinsulinaemia, stimulated by fetal hyperglycaemia and hyperaminoacidaemia, as proposed by Pedersen,<sup>3</sup> would lead to excess fat storage and fetal weight gain. In mothers with gestational diabetes mellitus, maternal triglyceride concentrations correlate more closely with fetal weight than maternal glucose concentrations, supporting the hypothesis that an excess of lipids might contribute to fetal weight gain.<sup>4</sup>

The neonatal dyslipidaemia Merzouk *et al* describe is intriguing, not least because it is associated with hyperinsulinaemia, rather than a relative hypoinsulinaemia akin to their mothers. The dyslipidaemia is similar to that found in type 2 diabetes and other insulin resistant states with hypertriglyceridaemia and low high density lipoprotein (HDL) cholesterol values.<sup>5</sup> It will be interesting to see whether the dyslipidaemia is maintained beyond infancy, or whether it is only a short term response to neonatal hyperglycaemia and hyperinsulinaemia.

Macrosomic babies of mothers without diabetes are hyperinsulinaemic.<sup>6</sup> In the study by Merzouk *et al* it is not possible to determine whether the macrosomic neonates born to the non-diabetic group have simply achieved their genetically determined birth weight or whether they are overly large. The normal plasma insulin concentration in this group would be consistent with appropriate rather than excessive growth.

A statistical correlation between low birth weight and impaired glucose tolerance in later life has been found and

confirmed in many studies.<sup>7</sup> Proponents of the “thrifty phenotype hypothesis” suggest a causative link between maternal nutrition, inadequate fetal growth, and disorders allied to insulin resistance in adulthood.<sup>8</sup> They propose that in utero starvation triggers permanent remodelling of physiology, “programming” these individuals to develop insulin resistance and related conditions such as type 2 diabetes. It is difficult to explain the relation of fetal macrosomia in mothers with gestational diabetes and type 2 diabetes in the offspring, but perhaps the association is not purely related to absolute body weight but more to fetal dysproportion. Others propose that the association between low birth weight and adult insulin resistance is genetically mediated.<sup>9</sup> Genetically determined insulin resistance could also result in low insulin mediated fetal growth in utero, as well as insulin resistance in childhood and adulthood. Low birth weight, measures of insulin resistance in life, and ultimately glucose intolerance, diabetes, and hypertension, would all be phenotypes of the same insulin resistant genotype. Central to this “fetal insulin hypothesis” is the concept that insulin mediated fetal growth will be affected by fetal genetic factors that regulate either fetal insulin secretion or the sensitivity of fetal tissues to the effects of insulin.

Merzouk *et al* have found dyslipidaemia in infants of mothers with poorly controlled type 1 diabetes. Does the genetic predisposition increase the risk of type 1 diabetes in the infant as in their mother; or does the dysnutrition increase the risk of insulin resistance and type 2 diabetes, unlike their mother, with impaired glucose tolerance in adulthood, or neither, or both? Although it may be premature to suggest that these results have implications for metabolic diseases in these infants, these studies may in time give insights into the differential effects of the metabolic milieu predisposing to impaired glucose tolerance in adulthood and also the genetic predisposition to impaired glucose tolerance in adulthood.

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