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Disturbances in lipid metabolism in diabetic pregnancy – Are these the cause of the problem?

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The most common neonatal complication of gestational diabetes (GDM) is macrosomia. During early pregnancy an accumulation of maternal fat depots occurs followed by increased adipose tissue lipolysis and subsequent hyperlipidaemia, which mainly corresponds to increased triglycerides (TG) in all circulating lipoproteins. In GDM women, the enhanced insulin resistance and decreased oestrogens are responsible for the reported wide range of dyslipidaemic conditions. In GDM, decreased proportion of long chain polyunsaturated fatty acids in fetus plasma could result from decreased supply, impaired placental transfer or even altered intrauterine metabolism. A positive correlation between maternal TG and neonatal body weight or fat mass has been found in GDM. Augmented oxidative stress and altered adipokines have also been found, with an adverse outcome even in normoglycaemic conditions. Thus, although additional studies are required, overall these findings indicate that altered maternal lipid metabolism rather than hyperglycaemia constitutes a risk for macrosomia in GDM.

Introduction

Despite advances in treatment, maternal diabetes during pregnancy is still associated with an unfavourable intrauterine environment for fetus development, increasing the risk of miscarriage, stillbirth, congenital malformations, placental dysfunction, fetus morbidity and mortality and

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intrauterine malprogramming.[1,2] Macrosomia or fetus obesity is a frequent complication in offspring of diabetes in pregnancy,[3] and macrosomic newborns incur a number of complications during both the prenatal and neonatal periods. Although the association of high maternal glucose levels and fetus macrosomia have been well documented,[4–6] fetus macrosomia is also observed in diabetic pregnancy with satisfactory glycaemic control.[7,8]

How maternal diabetes mellitus enhances lipid deposition in fetus adipose tissue is not yet understood. Conditions inducing enhanced adipogenesis are normally associated with the presence of a plethora of adipogenic substrates in the presence of a hyperinsulinemic milieu. In case of the fetus, the availability of substrates depends on their concentration in maternal circulation and to the extent that they are transported across the placenta. Both maternal hyperglycaemia and hypertriglyceridaemia are frequent in diabetic mothers as a consequence of their augmented insulin-resistant condition, and these changes would enhance the substrate availability to the fetus.[9,10] Both maternal triglycerides (TG) and non-esterified fatty acids (NEFA) levels but not glucose in pregnancies with well-controlled gestational diabetes mellitus (GDM) have been shown to correlate positively with both neonatal weight and fat mass,[11] indicating that maternal hyperlipidaemia in GDM actively enhances the availability of lipids to the fetus, contributing to his fat depot accumulation.

Changes in placental function must actively contribute to the enhanced flux of lipids to the fetus under the conditions of maternal diabetic hyperlipidaemia. Moreover, an altered handling or metabolism of fatty acids by the fetus of GDM women[12] could also contribute to disturbances in intrauterine fat deposition.

Hyperlipidaemia enhances the risk for oxidative stress and lipid peroxidation, and several studies have found associations among diabetes in pregnancy and various oxidative stress markers.[13,14] However, there is no consensus on the pathophysiological events underlying oxidative stress in diabetic pregnant women.

In an attempt to understand the potential role of disturbances of lipid metabolism under conditions of satisfactory glycaemic control as being responsible for the continuing high incidence of fetus macrosomia or dysfunctions in diabetic pregnancy, this chapter will review the principal aspects of lipid metabolism in normal and diabetic pregnancies and analyze its potential implication in birth weight disturbances.

Maternal lipid metabolism in normal pregnancy

The two consistent manifestations of altered maternal lipid metabolism during normal pregnancy are the accumulation of lipids in early pregnant maternal tissues[15] as result of major changes in adipose tissue metabolism and the later development of maternal hyperlipidaemia.[16]

Accumulation of maternal body fat

Fat accumulation in maternal depots is a characteristic feature of pregnancy[15] and takes place during the first two-thirds of gestation. Body fat accumulation during early pregnancy seems to be the result of both hyperphagia[17] and increased lipid synthesis.[18] It stops or even declines during the last third of gestation[15,19] as a consequence of both enhanced adipose tissue lipolytic activity (see below) and decreased adipose tissue lipoprotein lipase (LPL) activity, resulting in a net accelerated breakdown of fat depots. LPL is an enzyme, present in the capillary endothelium of extra-hepatic tissues, that hydrolyzes TG circulating in plasma in the form of TG-rich lipoproteins (i.e. chylomicrons and very low density lipoproteins, VLDL), and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue. Whereas no significant change has been found in the postheparin LPL activity in pregnant women at mid-gestation, it decreases during the third trimester of gestation,[16] and from studies in the rat it is known that such a change corresponds to a decreased adipose tissue LPL activity[20] which reduces the tissue uptake of circulating TG.

Adipose tissue lipolytic activity

Increased lipolysis of adipose tissue fat stores occurs during the last third of gestation.[21,22] The products of adipose tissue lipolysis, NEFA and glycerol, are released largely into the circulation. Since