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Placental dysfunction in obese women and antenatal surveillance strategies

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This review is aimed at discussing placental dysfunction in obesity and its clinical implication in pregnancy as well as an antenatal surveillance strategy for these women. Maternal obesity is associated with adverse perinatal outcome. Obesity is an independent risk factor for fetal hyperinsulinaemia, birthweight and newborn adiposity. Maternal obesity is associated with childhood obesity and obesity in adult life. Obesity induces a low-grade inflammatory response in placenta, which results in short- and long-term programming of obesity in fetal life. Preconception and antenatal counselling on obstetrics risk in pregnancy, on diet and lifestyle in pregnancy and on gestational weight gain is associated with a better outcome. Fetal growth velocity is closely associated with maternal weight and gestational weight gain. Careful monitoring of gestational weight gain and fetal growth, and screening and management of obstetrical complications such as gestational diabetes and pre-eclampsia, improves perinatal outcome. The use of metformin in non-diabetic obese women is under investigation; further evidence is required before recommending it.

Introduction

Obesity has become a global epidemic. It is estimated that 205 million men and 297 million women were obese in 2008 [1]. Obesity in pregnancy is defined as a body mass index (BMI) of $\geq$30 kg/m^2 at

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booking. One in five women in the UK is obese at antenatal booking; this is a threefold increase since 1980 [2]. Body fat distribution differs with race. Asian populations have more fat and more co-morbidity for any given BMI; therefore, it has been suggested to use lower BMI cut-off points for these populations [3]. Maternal obesity is associated with an increased risk of feto-maternal complications. Maternal obesity causes not only risks during the perinatal period but also long-term complications for the offspring. It creates a significant risk for the next generations with metabolic compromise already apparent at birth. The risks of developing adulthood obesity, hypertension, diabetes and metabolic syndromes are engineered in fetal life. The financial implications of obesity results in the rise in the health-care cost by 23% among overweight women and 37% among obese women after adjusting for maternal age, parity, ethnicity and co-morbidity, when compared with women with normal weight [4]. The present review is aimed at providing a comprehensive view on placental dysfunction in obese women and the need for antenatal surveillance strategies.

Molecular basis of placental dysfunction in obesity

In pregnancy, the feto-placental unit is a major site of protein and steroid hormone production and secretion, which results in metabolic changes. During in utero development, the fetus relies primarily on glucose as an energy substrate. There is a steady supply of glucose even during maternal fasting by increased hepatic gluconeogenesis in normal pregnancy. During early pregnancy, glucose tolerance is normal as insulin sensitivity and hepatic basal glucose production are normal [5,6]. In the second and third trimester, the feto-placental factors increase maternal insulin resistance, which is aimed at increasing the supply of glucose to the fetus [5,6]. Maternal oestrogen and progesterone promote pancreatic ß-cell hyperplasia causing an increased insulin release [7]. During pregnancy, the insulin resistance of the whole body is increased to about three times the resistance in the non-pregnant state [6,8]. In 2–4% of women, the pancreatic insulin response is inadequate to counterbalance the insulin resistance and gestational diabetes ensues. Maternal insulin resistance during pregnancy results in increased lipolysis with increased availability of free fatty acids (FFAs) to be used as adipogenic substrates in the fetus. Increased fetal adiposity and fetal insulin resistance are closely associated [5]. Obesity, independent of maternal glycaemia, is associated with fetal hyperinsulinaemia, birthweight, and newborn adiposity [9]. Although obesity and gestational diabetes share common metabolic pathways such as increased insulin resistance, hyperglycaemia and hyperinsulinaemia, they are independently associated with adverse maternal and neonatal outcomes. Their combination has a greater impact than either one alone [10]. In addition to hyperinsulinaemia, obesity induces exaggerated inflammatory responses in the placenta. The low-grade inflammation contributes to cellular dysfunction promoting metabolic disease [11,12]. There are various pathways suggested to explain the inflammatory state. The accumulation of a heterogeneous macrophage population and pro-inflammatory mediators in the placenta are suggested mechanisms. Nuclear factor kappaB (NFκB) and c-Jun N-terminal kinase (JNK) signalling pathways are the primary pathways of inflammatory responses [13]. The resulting inflammatory milieu in which the fetus develops may have critical consequences for short- and long-term programming of obesity [14]. The lipotoxic insults induce inflammation in placental cells via the activation of JNK/early growth response protein 1 (EGR-1) signalling [15]. The study shows gene expression for cytokines interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-8, and monocyte chemotactic protein 1 (MCP1); for lipopolysaccharide (LPS)-sensing CD14, Toll-like receptor 4 (TLR4), translocation associated membrane protein 2 (TRAM2) was 2.5–5-fold higher in the stromal cells of obese compared to lean women [16]. TLR4 has been implicated in the pathogenesis of FFA-induced insulin resistance. FFAs are ligands for the TLR4 receptor [17,18]. Excessive fatty acids in the fetal circulation due to maternal obesity are expected to activate TLR4, which results in inflammation by activating inhibitor of kappaB (IκB)/NFκB pathways. Abnormal TLR4 expression and signalling contribute to the pathogenesis of insulin resistance in humans [18]. Excess adipose tissue combined with low-grade inflammation and impaired insulin action is a central feature of the metabolic dysregulation in adult obesity. Maternal obesity enhances the expression of fatty acid transport proteins (FATPs), which increases fatty acid uptake and results in fetal adiposity at midgestation. These excessive fatty acids induce inflammation through the TLR4 pathway [18–21]. Low-grade maternal endotoxaemia is associated with insulin resistance and systemic inflammation in pregnant women with pre-gravid obesity [16]. Maternal obesity and change in placental metabolism strongly impact fetal redox