Pregnancy Outcome and Metabolic Syndrome

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13.1 Introduction

Obesity and metabolic disorders in women of reproductive age is a growing health problem; in the USA, pre-pregnancy obesity in women increased from 13.0% in 1993–1994 to 22.0% in 2002–2003, while the rate of obese European women ranges between 6 and 37% [1, 2].

Recent evidence indicates that approximately 10–30% of obese individuals have no metabolic abnormalities that describe MS (metabolic syndrome) such as impaired glucose tolerance, insulin resistance, dyslipidemia, and hypertension, so despite their excessive body fat, they are "metabolically healthy" [3].

Clinically, overweight risk may differ depending on body adipose tissue distribution, as central or "unhealthy" obesity leads to increased lipolysis, insulin resistance, and reduction of triglycerides storage, in contrast with lower limb adipose distribution with normal level of essential fatty acids (NEFA) or "healthy obesity" [4].

The ectopic fat accumulation is associated with lipotoxicity from lipid oxidation: the consequent oxidative stress causes maternal endothelial/vascular stress, increased inflammation, reduction of trophoblast invasion, and altered placental development [5]. Therefore maternal central obesity is associated with an increased risk of maternal and perinatal complications and also impacts the long-term health of the offspring leading to increased risk of childhood obesity and metabolic disorders given the critical role of intrauterine development [6, 7].

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13.2 Metabolic Syndrome, Obesity, and Pregnancy Complications

MS detection in pregnancy is a controversial issue, because the criteria for identifying MS overlap with the physiologic metabolic changes of pregnancy that disappear after delivery (insulin resistance, increased fat mass, hyperlipidemia, prothrombotic, and proinflammatory state) and some MS markers (obesity, high triglycerides, total cholesterol, and LDL cholesterol levels) show an increasing trend during gestation and there are no defined cut-offs in pregnancy [8].

Therefore there are very few studies about maternal metabolic syndrome in pregnancy examined as a whole phenotype and about its association with birth outcomes.

It is well known that obesity, as the main component of MS, is a relevant risk factor for pregnancy complications from conception to postpartum, and the risks are amplified with a higher maternal BMI. It has been estimated that one quarter of pregnancy complications are attributable to maternal overweight/obesity [9].

Overweight and obese women have an increased risk of spontaneous miscarriage [10] and congenital anomalies [11, 12], and the risks increase with the severity of obesity.

Obesity is strongly associated with the presence of gestational diabetes (GDM), preterm birth (both spontaneous and medically indicated), and intrauterine fetal death [13].

Compared with women with normal pre-pregnancy BMI, obese pregnant women are at increased risk of preeclampsia (PE) and gestational hypertension; the risk of preeclampsia rises as the pre-pregnancy BMI increases, and is closely associated with impaired insulin sensitivity [14, 15].

Several studies have confirmed that maternal obesity increases the risk of fetal macrosomia [16], independent of a diabetic metabolic state [17]. It has been demonstrated that offspring of obese mothers have a significantly higher percent of body fat mass and are more metabolically unhealthy (higher cord blood insulin, leptin, insulin resistance indexes, and IL6).

Furthermore, obesity is associated with increased risk of intrapartum complication; cesarean sections are more commonly performed in obese mothers due to preeclampsia, fetal distress, cephalopelvic disproportion, and failure to progress in labor [18, 19].

These women also have a higher incidence of wound infection and wound healing abnormalities with increased surgery-associated morbidity [20].

Only few studies to date have evaluated metabolic syndrome in pregnancy in relation to reproductive outcomes, and most of the authors have used accepted definition of MS for the adult population.

There is evidence that an unfavorable, atherogenic lipid profile during or prior to pregnancy is associated with increased risk for GDM, PE, large for gestational age (LGA) babies, and spontaneous preterm birth [21–23], and in a small prospective study, multiparous women with MS in early pregnancy had a threefold increased risk for preterm birth [24].

A recent study assessed the association between MS, measured at 15 weeks' gestation, and a range of pregnancy complications in low-risk, nulliparous women recruited to the multicenter, international prospective Screening for Pregnancy Endpoints (SCOPE) study. The research found that 12.3% of women had metabolic syndrome in early pregnancy defined according to the International Diabetes Federation criteria for adults. More than half of the women who had MS in early pregnancy developed a pregnancy complication, compared to one third of those who did not have MS [25].

In particular women with MS were at an increased risk for PE by a factor of 1.63 and for GDM by 3.71, after adjusting for a range of demographic and lifestyle variables; increase in BMI combined with MS increased the risk for GDM and decreased the probability of an uncomplicated pregnancy [26].

13.3 Inflammation, Insulin Resistance, and Oxidative Stress

Metabolic syndrome is characterized with a triad of closely linked metabolic aspects that are implicated in pregnancy complications: inflammation, insulin resistance, and dyslipidemia.

As an organ of exchange and dependent on maternal health, the placenta has a critical role in this metabolic milieu.

Placental dysfunction is implicated in most of the poor pregnancy outcomes associated with maternal obesity, such as preeclampsia or fetal growth anomalies, and is also known to be involved in the programming of later-life diseases.

Inflammation Obesity is a well-known low-grade inflammatory state and can interfere with placental development and function altering inflammatory pathways; it is associated with an increased production of pro-inflammatory mediators by macrophages in the adipose tissue, an increase in circulating levels of inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) [27, 28], and increased macrophage accumulation in both the adipose tissue and the placenta of obese pregnant women.

An increasing body of both experimental and clinical evidence suggests that pro-inflammatory cytokines stimulate signaling pathways in placental cells (trophoblasts, endothelial cells, and stromal cells), leading to cellular stress and dysfunction and influence placental nutrient transport functions [29, 30]. In particular IL-6 and TNFα stimulate amino acid transport [29, 31] and fatty acid uptake into primary trophoblasts [30].

This proinflammatory milieu in the placenta leads to the impairment of overall placental development and function and produces increased free fatty acid (FFA) delivery to the fetal circulation, which is expected to alter fetal growth and development [32], and has been linked to long-term changes in offspring metabolism [33].

Interesting studies have demonstrated that inflammation is active also in the vasculature of obese women and that it is associated with neutrophil infiltration. Specifically, the percentage of vessels stained for markers of inflammation was highly positively correlated with BMI. In summary, the vessel phenotype of obese

women appears to be very similar to the vessel phenotype of preeclamptic women, suggesting that vascular inflammation could act as the underlying connection between obesity and preeclampsia [34].

Insulin resistance Increased insulin resistance is part of the altered physiology of pregnancy. It is necessary to promote fetal growth and development. The physiologic rise in insulin resistance throughout the pregnancy slowly increases during the second half of pregnancy and rapidly decreases after delivery. The progressive insulin resistance during gestation involves a combination of increased maternal adiposity and the effects of the hormonal placental products. Obesity and metabolic syndrome before pregnancy are characterized by higher insulin resistance; therefore these women start pregnancy in a less insulin sensitive state.

It is well known that insulin resistance, together with a reduced beta cell capacity, is the most important feature in GDM pathogenesis and is therefore significantly associated with fetal overnutrition and macrosomia as a consequence of high fetal nutrient availability and placental transport of nutrients [35, 36]. Maternal hyperinsulinemia in the third trimester determines the activation of the main insulin signaling pathways in the placenta (p-ERK and p-Akt) and increases some placental lipid carriers, which might enhance fetal lipid transport and storage, resulting in increased fetal adiposity and probably contributing to the fetal programming of obesity [37].

Maternal insulin resistance has been hypothesized to contribute to altering placental development in pregnancies complicated by obesity and diabetes; in fact recent studies support an association between preeclampsia and increased insulin resistance [38–40], and reduced insulin sensitivity has also been hypothesized to contribute to the pathophysiology of the disease.

There is evidence from recent studies that increased insulin resistance has negative effects on placental growth and efficiency. It is well known that insulin may enhance villous proliferation and increase placental size determining a placental hypertrophy, which is a typical feature of diabetic pregnancies. However villous immaturity, defined as placentas with inadequate or absent terminal villi, was one of the most frequently reported placental abnormalities in pregnancies with increased insulin resistance [41, 42]. A high proportion of immature villi may decrease the efficiency of placental transport resulting in placental insufficiency [43] and consequently higher incidence of preeclampsia, fetal growth restriction, and fetal death.

Moreover insulin resistance can affect maternal endothelial function, and some data show that angiogenic and insulin-dependent pathways may influence each other [44, 45], and it is well known that dysfunction of the vascular endothelium and dysregulation of angiogenesis are thought to play a central role in the pathophysiology of preeclampsia.

Oxidative stress. Oxidative stress has recently been recognized as a key mechanism in insulin resistance; many studies demonstrated that increased oxidative stress is associated with insulin resistance pathogenesis by insulin signals inhibition and adipokine dysregulation [46, 47]. Several studies showed that reactive oxygen species (ROS) levels are increased in obesity, especially in abdominal obesity which is the major component of metabolic syndrome [48, 49].

Pregnancy itself is characterized by increased oxidative stress; in fact ROS regulate many cellular functions including autophagy, differentiation, and inflammation. Excessive ROS production can be harmful, causing oxidative damage to DNA, proteins, and cell membranes. There is evidence that increased placental oxidative stress is a mark of several obstetric pathologies including preeclampsia and intrauterine growth restriction (IUGR) in pregnancies complicated by maternal diabetes or obesity [50].

In recent years an association between chronic oxidative stress and placental senescence has been found; these aspects seem to have an important role in pathogenesis of placental insufficiency and preeclampsia [51, 52]. Moreover excessive ROS production in endothelium can affect vasodilation by inhibiting the expression and function of endothelial nitric oxide synthase [53] and may even be involved with this process in the pathogenesis of preeclampsia [54]. Obesity is associated with excess circulating fatty acids, which can affect placental mitochondrial function. In fact placental villous tissues from overweight and obese women have a 6- and 14-fold increase, respectively, in mitochondrial ROS production [55].

Though data may be limited, oxidative stress and mitochondrial dysfunction can be proposed as mechanisms that mediate placental dysfunction in maternal obesity and insulin resistance.

13.4 Prevention of Adverse Obstetric Complications

Both lifestyle (diet and physical exercise) and pharmacological interventions (metformin, inositol) have been suggested to prevent the development of metabolic complications.

The majority of studies on dietary and lifestyle interventions during pregnancy failed to show significant benefits in maternal and fetal outcomes; potential reasons for these results include the substantial heterogeneity between the characteristics of the participants, the interventions, the settings, the inability to estimate patient adherence, and a tardy intervention start during gestation.

Pre-conceptional and interpregnancy periods should focus on promoting maternal weight loss in overweight and obese women, which may potentially reduce the risk of gestational diabetes and LGA, even with moderate changes [56, 57]. If weight loss is not achieved, it is also important to avoid at least weight gain between pregnancies, as gestational diabetes risk directly increases with a rise in BMI in retrospective cohorts [58].

Concerning polycystic ovary syndrome (PCOS), a recent metanalysis of 12 RCTs comparing 608 women has demonstrated the efficacy of lifestyle interventions plus metformin vs lifestyle interventions plus placebo. Both approaches were significantly associated to lower BMI, lower subcutaneous adipose tissue, and increased number of menstrual cycles after 6 months [59]. Myo-inositol acts on a side pathway influencing insulin sensitivity, and randomized controlled trials have reported its efficacy in reducing basal insulin levels, testosterone concentration, and HOMA index in PCOS [60]. The importance of a pre-conceptional period is

underlined by the observation that diet and physical activity in obese women during pregnancy are poorly associated with prevention of adverse outcomes, such as gestational diabetes, as reported by the Limit Study [61, 62]. Multicenter and individualized interventional studies have extended observation to FPG, maternal-neonatal outcomes, risk of CS, and HOMA-IR, demonstrating that in-pregnancy intervention results in no significant preventive effects [63, 64]. According to the Cochrane review on 23 RCTs, the prevention of gestational diabetes mellitus in pregnancy is only potentially associated with reduction in CS, but not with the rate of PE, LGA, and perinatal mortality [65]. In-pregnancy interventions for obese women may be directed toward preventing excessive weight gain rather than reducing BMI, as a gestational weight gain of over 5 kg has been reported as a risk factor for macrosomia (87.8% sensitivity, 54.7% specificity) and hypertensive disorders of pregnancy (70% sensitivity, 48.4% specificity) [66].

The favorable effects of metformin on pregnancy outcome have been extensively studied both in obese and PCOS women. Even if meta-analyses have reported a consistent reduction of GDM risk, recurrent pregnancy loss, and preterm birth [67], other experiences provide conflicting data [68, 69]. One of the most interesting effects of metformin on obese and hyperinsulinemic patients is the prevention of preeclampsia: the reduction of the inflammation state and improvement of endothelial cell function reduce the expression of vascular cell adhesion molecules, and the support of the whole-blood vessel angiogenesis is able to reduce production of sFlt-1 and soluble endoglin, which are strictly involved in the pathogenesis of preeclampsia [35, 70]. Metformin has been suggested to potentially improve the offspring body composition at 2 years of age after gestational diabetes when compared with insulin, lowering the mid-upper arm circumferences, the subscapular, and biceps skinfolds, thus regulating fat distribution by reducing the visceral fat deposition [71]. Nevertheless, long-term effects have not yet been studied.

Myo-inositol is a post-receptorial mediator of insulin. It translocates GLUT4 receptor on the cell membrane and participates in the cholinergic way of insulin secretion [72]. RCTs have reported that its prenatal supplementation is associated with reducing the GDM rate, but has no effect on gestational hypertension, LGA, perinatal mortality, or composite severe neonatal outcome [73–76].

Aspirin seems promising for preventing preeclampsia also in obese women: a body mass index >30 kg/m^2 is classified as a moderate risk factor by ACOG and may be considered a clinical indication for prophylactic administration [77].

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