Focus on Obesity

Obesity, insulin resistance, and pregnancy outcome

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Abstract

There has been a significant increase over the past few decades in the number of reproductive age women who are either overweight or obese. Overweight and obese women are at increased risk for having decreased insulin sensitivity as compared with lean or average weight women. The combination of obesity and decreased insulin sensitivity increases the long-term risk of these individuals developing the metabolic syndrome and associated problems of diabetes, hypertension, hyperlipidemia, and cardiovascular disorders. Because of the metabolic alterations during normal pregnancy, particularly the 60% decrease in insulin sensitivity, overweight and obese women are at increased risk of metabolic dysregulation in pregnancy, i.e. gestational diabetes, preeclampsia, and fetal overgrowth. Hence, pregnancy can be considered as a metabolic stress test for the future risk of the metabolic syndrome. In this review, we will review the underlying pathophysiology related to these disorders. Most importantly, an understanding of these risks provides an opportunity for prevention.

For example, a planned pregnancy offers an opportunity to address weight control prior to conception. At the very least, by avoiding excessive weight gain during pregnancy, this may prevent excessive weight retention post partum. Finally, based on the concept of in utero programming, these lifestyle measures may not only have short- and long-term benefits for the woman but also for her offspring as well.


Obesity

There has been a significant increase in obesity in the last 40 years not only in developed areas of the world but also in developing countries (World Health Organization 2000). In the United States, ~62% of the female population > 20 years of age are overweight and 33% are obese, based on WHO body mass index (BMI, kg/m²) criteria (Ogden et al. 2006). Furthermore, 6.9% of the female population have a BMI > 40, or Class III obesity (Ogden et al. 2006). In Asian populations, because of differences in body composition, the criteria for risk of metabolic dysfunction such as diabetes and cardiovascular disease are different than in a Caucasian population. A BMI of 23–27.5 is designated as increased risk, and a BMI > 27.5 is designated as high risk for metabolic dysfunction (WHO Expert Consultation 2004). Approximately 11% of US children are obese based on the Center for Health and Disease Criteria (CDC), i.e. weight for height > 2 s.d.s for age and gender (Ogden et al. 2008). Last, there has been reported a significant increase in the mean term birth weight in various North American and European populations (Ananth & Wen 2002, Surkan et al. 2004).

Although BMI is a commonly used clinical criterion for obesity, in pregnancy, BMI is a less robust estimate of adiposity. This is because on the physiological changes in pregnancy, specifically the significant increases in total body water. There is a decrease in the hydration constant of fat free mass from 76% in nonpregnant individuals to ~72% in late gestation (Catalano et al. 1995a, 1995b). The correlations of BMI with measures of body composition decrease with advancing gestation, from $R^2 = 0.86$ pregravid to $R^2 = 0.54$ in the third trimester (Sewell et al. 2007). Similarly, in neonates, the ponderal index (weight (g)×100/length (cm)) is a frequently used measure of obesity at birth. However, as with BMI, the ponderal index accounts for only a fraction (15%) of the variance in adiposity in the neonate (Catalano et al. 1992).

Insulin resistance

Decreased insulin sensitivity or increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g. liver, muscle, or adipose tissue. Obesity is the most common risk factor related to decreased insulin sensitivity. The resistance to insulin...
can be characterized as pre-receptor (insulin antibodies), receptor (decreased number of receptors on the cell surface), or post-receptor (defects in the intracellular insulin signaling pathway). In pregnancy, the decreased insulin sensitivity is best characterized as a post-receptor defect resulting in the decreased ability of insulin to bring about SLC2A4 (GLUT4) mobilization from the interior of the cell to the cell surface. Although human placental lactogen has often been cited as the cause of the decreased insulin sensitivity of pregnancy, because of its production from the placenta and increasing concentrations with advancing gestation (Ryan & Enns 1988), more recently the role of cytokines and elevated lipid concentrations in pregnancy have been correlated with the longitudinal changes in insulin sensitivity in nonpregnant women (Hotamisligil et al. 1994) as well as in pregnant women (Xiang et al. 1999, Kirwan et al. 2002). A potential mechanism for tumor necrosis factor-α affecting the post receptor insulin signaling cascade in skeletal muscle resulting in decreased insulin sensitivity is shown in Fig. 1.

Insulin sensitivity in vivo during pregnancy can be estimated using a variety of techniques. The gold standard, however, is the hyperinsulinemic–euglycemic clamp techniques as described by DeFronzo et al. (1985). In this technique, insulin is infused as a primed constant infusion in order to attain a steady-state insulin concentration. A variable glucose infusion is then based on frequent glucose sampling in order to maintain a constant euglycemic glucose concentration, i.e. the glucose is clamped at a steady-state level. Stable isotopes of glucose, lipids, and amino acids can be incorporated with the clamp technique to measure specific turnover rates of individual nutrients and tissues relative to the specific action of insulin, e.g. gluconeogenesis or lipolysis. Because of the complexity, expense, and time involved in the hyperinsulinemic–euglycemic clamp, this methodology is primarily used in research studies when accuracy and reproducibility of the measures are required. The minimal model developed by Bergman et al. (1987) estimates insulin sensitivity using an i.v. glucose tolerance test. The minimal model may be less useful in late pregnancy because of the decreased insulin sensitivity in late gestation. The minimal model has increased variability when estimating insulin sensitivity in late gestation in comparison with the euglycemic clamp. More common clinical methods include measures of fasting glucose and insulin (HOMA (homeostasis model assessment) and QUICKI (quantitative insulin sensitivity check index); Matthews et al. 1985, Katz et al. 2000) as well as models using the oral glucose tolerance test, e.g. as described by Matsuda & DeFronzo (1999). However, all these methodologies have limitations. During pregnancy, there is noninsulin-mediated glucose disposal from the mother to the fetus through placental facilitated diffusion of glucose. Therefore, all estimates of insulin sensitivity in pregnancy are overestimates of maternal insulin sensitivity, particularly in late gestation.

Figure 1 Proposed mechanism by which tumor necrosis factor-α (TNF) may decrease insulin sensitivity. TNF activates a pathway that increases sphingomyelinases and ceramides, and may interfere with insulin receptor 1 (IRS1) autophosphorylation.

Figure 2 Insulin sensitivity in i.v. glucose tolerance assessed by minimal model analysis in women with preeclampsia and normotensive control women (A) during pregnancy and (B) 12 weeks after delivery. Data are mean ± S.E.M. Reproduced from Kaaja R, Laivuori H, Laakso M, Tikkanen MJ & Ylikorkala O 1999 Evidence of a state of increased insulin resistance in preeclampsia. Metabolism 48 892–896, with permission from Elsevier. © 1999 Elsevier.
Maternal metabolic complications of obesity

Women who are obese and therefore more likely have decreased insulin sensitivity are at increased risk for many adverse pregnancy outcomes. Similar to what is observed in the nonpregnant population, the constellation of conditions mimics the metabolic syndrome (World Health Organization 1999). The metabolic syndrome of pregnancy includes an increased risk of hypertensive, metabolic disturbances of nutrient metabolism, and inflammation. Although these pregnancy-related conditions are most likely to clinically resolve once the woman is delivered, these individuals still have the subclinical underlying metabolic disorder, and are at increased risk for the metabolic syndrome in later life, particularly if there is increased postpartum weight gain (Villamor & Cnattingius 2006).

Hypertensive disease

Obese women have a 10–15% increased risk for preeclampsia (Barton & Sibai 2008). The decreased insulin sensitivity is manifest as early as the first trimester of pregnancy. Wolf et al. (2002) reported that sex hormone-binding globulin as a marker of decreased insulin sensitivity was significantly decreased in nulliparous women during the first trimester that eventually went on to develop preeclampsia as compared with a control group. Furthermore, when stratifying the women based on BMI, overweight women had lower sex hormone-binding globulin concentrations as compared with lean women and within each stratum of BMI (Wolf et al. 2002). Similarly, Mazaki-Tovi et al. (2009) using measures of serum adiponectin, a cytokine associated with increased insulin sensitivity, reported that in women with mild preeclampsia, there were decreased concentrations of high-molecular weight adiponectin, the most active form of adiponectin, in comparison with normotensive pregnant women. In contrast to decreasing concentrations of circulating adiponectin with advancing gestation, preeclampsia was not associated with decreased adiponectin in overweight and obese women. Using the minimal model technique, Kaaja et al. showed that in late gestation women, developing preeclampsia have decreased insulin sensitivity as compared with a control group matched for BMI and other potential confounding variables (Fig. 2A). Consistent with the decreased insulin sensitivity, the women developing preeclampsia also had elevated free fatty acid, triglycerides, and C-peptide concentrations. Although there was the expected improvement in insulin sensitivity post partum, the women developing preeclampsia had decreased insulin sensitivity (Fig. 2B) that persisted for at least 3 months (Kaaja et al. 1999). Taken as a whole, these studies are consistent with the concept of obesity and insulin resistance as putative factors related to the development of preeclampsia. Of interest is the decreased insulin sensitivity which is present in early in gestation, prior to the clinical manifestations of the disorder, and persists post partum, thereby providing a link between the pregnancy-related hypertensive disorders of pregnancy and later manifestations of the metabolic syndrome. Much as with the mechanism associated with decreased insulin sensitivity and essential hypertension, the underlying mechanisms related to the development of preeclampsia is not very well characterized (Solomon & Seely 2001).
glucose tolerant women and those developing GDM, overweight and obese women have decreased insulin sensitivity as compared with lean or average weight women, although both groups have a similar 50\% decrease over the period of gestation (Fig. 5; Catalano & Ehrenberg 2006). Hence, just as there has been an increase in the number of individuals classified as having either impaired fasting glucose (33.8\%) or impaired glucose tolerance (15.4\%; Center for Disease Control and Prevention 2007), the number of women with GDM presently at 5–10\% of the population may significantly increase based on the recommendations of the International Diabetes in Pregnancy Study Group (International Association of Diabetes and Pregnancy Study Groups Consensus Panel 2010). These data are also consistent with the underlying pathophysiology of GDM resulting in a 50–60\% increase in type 2 diabetes in 10 years after the diagnosis of GDM (Kim et al. 2002).

**Hyperlipidemia**

The decrease in insulin sensitivity in pregnancy is not limited only to glucose metabolism but is also observed in relation to lipid metabolism as well (Catalano et al. 2002). There is a two- to threefold increase in basal triglyceride and cholesterol concentrations with advancing gestation (Knopp et al. 1980). The increases are more pronounced in the GDM as compared with the normal glucose tolerant pregnant woman (Catalano et al. 2002). The increase in free fatty acid concentration is related to the decreased ability of insulin to suppress lipolysis in late gestation. Freinkel (1980) coined the term ‘accelerated starvation of pregnancy’ to describe the increasing risk of ketosis observed in pregnant women. The increased free fatty acids are then useful for providing an energy source for maternal needs in late gestation when maternal energy requirements are greatest. The increase in free fatty acids may also play a role in excessive fetal growth. Although the increased glucose concentrations in pregnancy observed in obese and GDM women are a stimulus for fetal insulin production, the nutrient substrates for fetal growth in particular adiposity are less well described.

**Figure 5** The longitudinal changes in insulin sensitivity in average (BMI < 25), overweight (BMI 25–30), and obese (BMI ≥ 30) women over time. Early pregnancy, 12–14 weeks and late pregnancy, 34–36 weeks; longitudinal changes over time, P = 0.0004. Adapted, with permission, from Catalano PM & Ehrenberg HM 2006 The short- and long-term implications of maternal obesity on the mother and her offspring. British Journal of Obstetrics and Gynecology 113 1126–1133. © 2006 RCOG.

**Glucose intolerance/gestational diabetes**

Obesity is the strongest risk factor for the development of type 2 diabetes in the nonpregnant individual and for the development of glucose intolerance during gestation, i.e. gestational diabetes (GDM). The underlying metabolic defects related to the development of both these disorders are decreased insulin sensitivity coupled with an inadequate insulin response (Buchanan & Xiang 2005). In prospective longitudinal studies, our group has shown that women with normal glucose tolerance have a 50–60\% decrease in insulin sensitivity during the course of gestation (Fig. 3; Catalano et al. 1991). When compared with weight matched controls, women with normal glucose tolerance prior to conception and go on to develop GDM during pregnancy have significant decreased insulin sensitivity both before and during pregnancy (Fig. 4; Catalano et al. 1999). However, both groups have a similar percent decrease in insulin sensitivity. Similar as to what was observed in normal

**Figure 6** Body composition in neonate of women with normal glucose tolerance (NGT) and gestational diabetes (GDM). Lean body mass (LBM), P = 0.74; fat mass (FM), P = 0.0002; percent body fat (%BF), P = 0.0001. Adapted from Catalano PM, Thomas A, Huston-Presley L & Amini SB 2003 Increased fetal adiposity: a very sensitive marker of abnormal in utero development. American Journal of Obstetrics and Gynecology 189 1698–1704, with permission from Elsevier. © 2003 Elsevier.
Recent studies by Di Cianni et al. (2005) and Schaefer-Graf et al. (2008) have reported a significant correlation between maternal triglyceride concentration in late pregnancy and fetal growth/adiposity. Consistent with these clinical observations, Radaelli et al. (2009) have reported that enzymes related to intermediary lipid metabolism in contrast to glucose are increased in placenta of obese GDM women. These data support the concept that the elevated lipid concentration in obese women with GDM reflects a metabolic stress test for those disorders in mother and her fetus. For the obese women with subclinical decreased insulin sensitivity, pregnancy represents a metabolic stress test for those disorders in pregnancy, which are the harbingers of the metabolic syndrome in later life, e.g. GDM and preeclampsia. As a consequence, offspring of obese women are at increased risk of indicated preterm delivery and associate neonatal syndrome.

Body composition

The assessment of fetal growth has been variously classified over time. Initially, any small baby was classified as ‘preemie’, whereas large babies were classified as ‘macrosomic’. In the latter part of the last century, it became more common to classify fetal growth or birth weight as a function of gestational age. Birth weights for gestational age were categorized as percentiles with the small being arbitrarily defined as less than the 10th percentile (small for gestational age) and large as greater than the 90th percentile (large for gestational age).

A further refinement of growth includes the estimation of body composition, i.e. the description of lean and fat mass. In contrast to most mammals at birth, the human has a large proportion of birth weight as fat mass, ~10–12%. In contrast, most murine models have only 1–2% body fat, whereas nonhuman primates have only 3–5% body fat (Widdowson 1950, Russo et al. 1980, Ausman et al. 1982). Based on studies by Sparks (1984), lean body mass has a stronger correlation with genetic factors, while fat mass may relate more to the maternal environment. Therefore, the use of body composition is important in assessing fetal growth relative to the in utero environment.

It has long been recognized that infants of GDM and obese women weigh more at the birth than either women with weight-matched normal glucose tolerance or normal weight women respectively. Based on studies by our group and others, the infant of the GDM weighs more at birth because of an increase in fat mass and not lean body mass (Fig. 6; Catalano et al. 2003). Similarly the offspring of the obese women weighs more at birth because of increased fat mass and not lean mass (Fig. 7; Sewell et al. 2006). The strongest correlate with neonatal fat mass in women with GDM is decreased maternal pregravid insulin sensitivity (Catalano et al. 1995a, 1995b). In obese women, maternal pregravid BMI, as a surrogate for insulin resistance, has the strongest correlation with neonatal adiposity (Catalano & Ehrenberg 2006). The increased adiposity at birth is also a risk factor for childhood obesity and long-term metabolic dysfunction (Catalano et al. 2009).

Summary

Maternal obesity and underlying insulin resistance are significant short- and long-term risk factors for both the mother and her fetus. For the obese women with subclinical decreased insulin sensitivity, pregnancy represents a metabolic stress test for those disorders in pregnancy, which are the harbingers of the metabolic syndrome in later life, e.g. GDM and preeclampsia. As a consequence, offspring of obese women are at increased risk of indicated preterm delivery and associate neonatal syndrome.
morbidity. These children are also at risk for childhood metabolic dysfunction, which creates the potential of a vicious cycle of obesity and insulin resistance begetting obesity and metabolic dysfunction (Fig. 8; Catalano 2003). Hence, lifestyle intervention of diet, exercise, and weight control, ideally before and at the very least during gestation, offers the potential of benefit for both short- and long-term benefit for the mother and her child.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this work.

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