Gestational diabetes (GDM) complicates 3–12% of all pregnancies and the prevalence in the United States has doubled as a result of the growing obesity epidemic and changes in diagnostic criteria (Kaufmann et al., 1995). The immediate sequelae for the fetus are fetal hyperinsulinaemia, macrosomia, delayed lung maturation, an increased risk of shoulder dystocia and newborn metabolic abnormalities, including neonatal hypoglycaemia. The mother experiences an increased risk of caesarean section, infectious complications and pre-eclampsia (Barbour and Reusch, 2001). However, the long-term implications may be more grave and include a 50% risk of the development of Type 2 diabetes (DM) in the mother. In a sense, pregnancy is a ‘stress test’ for the development of Type 2 DM. New data suggest that the offspring may also be vulnerable to the in-utero exposure of excess nutrients and have an increased risk of obesity, impaired glucose intolerance and Type 2 diabetes as young adults (Silverman and Metzger, 1995; Dabelea et al., 2000). We have been only modestly effective in reducing the incidence of macrosomia in these infants, in spite of attempts at strict metabolic control in the mother. Thus, there remains a complete lack of consensus internationally regarding the resources that should be committed to the diagnosis and treatment of this condition in pregnancy. However, some might argue that our inability to impact macrosomia may be due to a misdirected focus on maternal glycaemia alone rather than fetal indicators of nutrient excess. Although the normal insulin resistance of pregnancy appears to benefit the fetus by assuring its adequate nutrition, these adaptations result in a pathological state if nutrition, these adaptations result in a pathological state of obesity, impaired glucose intolerance and Type 2 diabetes. The Frienkel hypothesis of fuel-related teratogenesis suggests that maternal fuels modify phenotypic gene expression in terminally differentiated cells in utero. Evidence to support this hypothesis includes the observation that elevated amniotic fluid insulin levels (due to maternal hyperglycaemia) predicted a 10-fold increase in teenage obesity in one study, independent of fetal weight, and one-third of these offspring had impaired glucose tolerance by 17 years of age (Silverman and Metzger, 1995). Pima Indians have an extraordinarily high genetic predisposition to develop Type 2 diabetes and childhood Type 2 diabetes has doubled in this decade (Dabelea et al., 2000). This population offers a unique opportunity to try to separate out the genetic influence versus the environmental influence of in-utero exposure to hyperglycaemia. The incidence of childhood Type 2 diabetes was determined in offspring born to mothers who had gestational diabetes (offspring of diabetic mothers) vs. the offspring of mothers who developed Type 2 diabetes after the pregnancy but did not have GDM (offspring of pre-diabetic mothers). The genetic risk for Type 2 diabetes to the offspring of these mothers should be roughly equivalent, with the only difference being the presence or absence of in-utero exposure to hyperglycaemia and other excessive nutrients. The incidence of childhood Type 2 DM was ~10-fold higher in Pima offspring of diabetic mothers (~10% vs. ~1%) compared to the offspring of prediabetic mothers. Furthermore, in spite of a similar incidence of obesity at 20 years of age between the two groups, the incidence of Type 2 DM was ~70% at age 25–29 years in the offspring of diabetic women with a history of GDM who continue to have impaired glucose tolerance postpartum have an exceedingly high risk of developing Type 2 diabetes, estimated at 80% in 5–10 years at a rate of ~16% per year in one study of Latino women (Kjos et al., 1995). Women with gestational diabetes who continue to demonstrate impaired glucose tolerance postpartum are a critical group to identify and target primary prevention efforts. In the United States, the new diagnosis of Type 2 diabetes in the 30–39-year age group has risen by 70% in this decade and by 300% in adolescents (CDC, 2000). Furthermore, fetal imprinting appears to occur in this intrauterine environment of nutrient excess and the offspring represent a high-risk group for the development of childhood obesity and glucose intolerance. 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Insulin resistance of normal pregnancy

Pregnancy is a complex metabolic state that involves dramatic alterations in the hormonal milieu (increases in estrogen, progesterone, prolactin, cortisol, human chorionic gonadotrophin, placental growth hormone and human placental lactogen) as well as an increasing burden of fuel utilisation by the conceptus. The insulin resistance of normal pregnancy that occurs in the second and third trimester is advantageous. It is mediated by placental hormones and is a physiological adaptation that ensures that maternal glucose will be diverted adequately to the fetus to meet the nutritional and growth demands. Although this insulin resistance has been well described, the hormonal mechanisms by which this insulin resistance is triggered remain enigmatic. Normal pregnancy is characterised by a ~50% decrease in insulin-mediated glucose disposal in humans and rodents (assessed by the hyperinsulinaemic–euglycaemic clamp technique) and a 200–250% increase in insulin secretion (Kuhl, 1998; Catalano et al., 1999; Yamashita et al., 2000). Hepatic glucosegenesis is not normally suppressed by insulin. This serves to meet the metabolic demands of the fetus, of which 80% of the fetal energy source is glucose, yet maintains euglycaemia in the mother (Aldoretta and Hay, 1995). It has been demonstrated that in normal pregnancy, there is decreased expression of the GLUT-4 glucose transporter protein in maternal adipose tissue (Garvey et al., 1993; Okuno et al., 1995) but not in skeletal muscle. Skeletal muscle is the principal site of insulin-mediated glucose disposal in vivo, suggesting that the mechanisms behind insulin resistance in skeletal muscle lie in the pathways for insulin signalling or abnormal translocation of GLUT-4 (Friedman et al., 1999).

Progress in defining the possible mechanisms underlying insulin resistance has been advanced by an increasing understanding of insulin action. A number of key events must follow sequentially in order for insulin to increase glucose uptake into its target tissue. The initial step involves insulin binding to its receptor, resulting in autophosphorylation of the intracellular (beta) subunit of the receptor. A downstream docking protein, called insulin-receptor-substrate-1 (IRS-1) is the chief substrate for this tyrosine kinase, which becomes tyrosine-phosphorylated upon its interaction with the insulin receptor. For glucose transport to occur, IRS-1 must bind to the p85 α subunit of a critical effector molecule called phosphotyidylinositol (PI) 3-kinase and tyrosine-phosphorylate it. The formation of a critical effector molecule called phosphotidylinositol (PI) 3-kinase and tyrosine-phosphorylation of IRS-1 (Shao et al., 2000). Recent data in pregnancy also demonstrate increases in serine phosphorylation of the insulin receptor, which may prevent optimal binding of IRS-1 to PI 3-kinase resulting in inhibition of GLUT-4 translocation (Shao et al., 2000).

Possible role of human placental growth hormone in mediating the insulin resistance of pregnancy

What causes the insulin resistance of normal pregnancy is still a subject of debate. Also unknown is whether excessive stimulation of those pathways inducing the physiological insulin resistance of pregnancy could lead to gestational diabetes, or whether some additional genetic abnormalities which predate the pregnancy and are independent of this adaptation are required. Historically it has been accepted that human placental lactogen (hPL) is the major insulin resistance hormone of pregnancy (Handwerger and Free- mark, 2000). Human placental lactogen can be detected in the syncytiotrophoblast at 5–10 days and peaks at 30 weeks and has been shown to have both insulin and anti-insulin effects (Anthony et al., 1998). In transgenic mice over-expressing hPRL, pancreatic beta cell proliferation in rats results in increased islet cell mass and hypoglycaemia over the long term (Breij et al., 1993). Therefore, the major role of hPL may be to induce the adaptive increase in insulin secretion necessary for pregnancy rather than induce insulin resistance. Recently, tumour necrosis factor-alpha (TNF-α) was demonstrated to have a strong correlation with the insulin resistance of pregnancy, and the role of this hormone remains to be elucidated (Kirwan et al., 2002).

Human placental growth hormone (hPGH) is an attractive candidate to mediate the insulin resistance of pregnancy, given the known diabetogenic effects of chronically elevated levels of pituitary growth hormone. Human placental growth hormone differs from pituitary growth hormone by 13 amino acids (Evain-Brion et al., 1994; Alsat et al., 1998). It is not regulated by GHRH or inhibited by somatostatin analogues, but has the same avidity for the GH receptor as pituitary GH. It is secreted tonically rather than in a pulsatile fashion, unlike pituitary GH, and by 20 weeks’ gestation replaces pituitary GH almost completely in the maternal circulation. Human placental GH does not cross the placenta and appears to regulate the maternal levels of IGF-1. Maternal IGF-1 levels in plasma correlate with hPGH levels, not with hPL. Transplacental glucose and amino acid transport is regulated by IGFs and have been shown to increase fetoplacental amino acid uptake in sheep and promote vasodilation of the placenta affecting the supply of nutrient availability for the growth of the fetus (Zumkeller, 2000). Human placental growth hormone appears to be a paracrine growth factor and through insulin growth factors may regulate partially the metabolic and growth effects of the fetus.

We have demonstrated recently that the human placental growth hormone is a metabolically active hormone capable of causing severe insulin resistance in transgenic mice which express this hormone at levels similar to the third trimester of human pregnancy (Barbour et al., 2002). These mice demonstrate severe insulin resistance exhibited by both fasting and post-prandial hyperinsulinaemia and require insulin levels that are five to seven times higher in order to maintain euglycaemia. Similarly, insulin mediated glucose
disposal is decreased markedly with no significant change in glucose levels, despite insulin dosing that results in a 50% decrease in glucose in their wild-type littersmates. These mice also demonstrate a marked decrease in insulin-induced GLUT-4 translocation to the plasma membrane. Additionally, we have found that the skeletal muscle tissue of these mice demonstrate abnormalities in insulin signalling which bear a remarkable similarity to that found in normal pregnant women and pregnant women who develop gestational diabetes. These data suggest that human placental growth hormone may be responsible for mediating a significant degree of the insulin resistance of normal pregnancy.

Insulin resistance in gestational diabetes—evidence for defects pre-dating pregnancy

Pregnancies complicated by gestational diabetes (GDM) are characterised by further insulin resistance and an inability to increase insulin secretion to compensate for this defect (Kuhl, 1998; Catalano et al., 1999; Yamashita et al., 2000). The pancreatic beta cell secretory defect is present in both obese and lean women with GDM; however, it is most pronounced in lean women with GDM who do not appear to have as marked insulin resistance as obese women who develop GDM (Kuhl, 1998; Catalano et al., 1999; Yamashita et al., 2000). Recent data demonstrate that overweight women destined to develop GDM demonstrate insulin resistance prior to pregnancy as measured by a hyperinsulinaemic–euglycaemic clamp (Catalano et al., 1999). Insulin-mediated glucose disposal continues to decrease in the second and third trimester of pregnancy and is about two-thirds that of normal pregnant women matched for weight. Furthermore, although women with GDM improve their insulin resistance postpartum, they never achieve the same degree of insulin-mediated glucose disposal as do normal pregnant women. Recent progress has shown that the mechanisms for skeletal insulin resistance in obese women with GDM involves impaired insulin receptor β-subunit tyrosine-phosphorylation and decreased IRS-1-phosphorylation and expression when muscle fibres in pregnant women undergoing caesarean section were examined (Friedman et al., 1999; Shao et al., 2000). There was a modest but significant decrease in maximal insulin receptor tyrosine-phosphorylation in muscle from obese GDM women compared to obese pregnant patients (Okuno et al., 1995; Friedman et al., 1999). This insulin receptor tyrosine kinase activity (IRTK) catalyses the phosphorylation of various insulin receptor substrates, particularly IRS-1, to undergo tyrosine-phosphorylation. While insulin receptor tyrosine-phosphorylation is impaired in GDM patients only, IRTK is reduced significantly by 23% in pregnancy and reduced severely by 41% in GDM patients compared to obese non-pregnant controls in these muscle fibres. Overall, these data point to a possible insulin receptor defect that may exacerbate the physiological effects of normal pregnancy.

Failure to prevent macrosomia and the ‘fetoplacental glucose steal’ syndrome

Macroism is the major risk to the fetus in women with GDM. Many theories have been generated over the years to explain the macrosomia associated with diabetes in pregnancy. Overall, the theory of excessive fetal insulin due to increased transport of maternal fuel to the conceptus holds the most credence and has the most supportive data (Pederson’s hypothesis). Diabetes in pregnancy is associated with increased delivery of glucose and amino acids to the fetus via the maternal circulation. These fuels can stimulate increased production of fetal insulin, which promotes somatic growth. Other maternal substrates (e.g. free fatty acids and triglycerides) add to the burgeoning supply of fetal substrate and further support excessive growth. It is, therefore, the goal of management of GDM pregnancies to normalise the fasting and postprandial glucoses to achieve good metabolic control. However, maternal obesity appears to be an independent risk factor for macromomia because some mothers who appear to have optimal metabolic control still give birth to macromomic infants. Furthermore, macrosomia is not limited to the diabetic population; in fact, approximately 25% of macromomic infants are born to mothers without GDM. It has been shown recently that women may have glucoses within the target range yet there is excess shunting of glucose to the fetus, as demonstrated by increased amniotic fluid insulin levels reflecting fetal hyperinsulinaemia (Weiss et al., 2001). Women who demonstrate the highest amniotic fluid insulin levels reflecting fetal hyperinsulinaemia as a response to maternal hyperglycaemia may actually have lower glucoses on a follow-up glucose tolerance test than women who demonstrate normal amniotic fluid insulin levels (Weiss et al., 2001). Thus, fetal hyperinsulinaemia masks maternal hyperglycaemia and appears to result in a ‘fetoplacental glucose steal’ syndrome (Weiss et al., 2001). Given normal maternal glucoses levels, one could argue falsely that the fetus is not a risk for macrosomia when in fact the placenta is shunting maternal glucose, resulting in hyperinsulinaemia and excessive fetal growth. The changes in placental-glucose transport in these pregnancies has not yet been examined to determine whether there is an increase in GLUT-1 transport earlier in pregnancy (Gaither et al., 1999).

Use of fetal criteria to direct management in gestational diabetes

As a result of our limited ability to decrease the incidence of macromomia in women with GDM by using maternal glucoses alone to dictate intervention, Buchanan randomised GDM women with normal target fasting and postprandial glucoses to insulin vs. no therapy if there was evidence of body-to-head disproportion by a 29–33-week growth scan (Buchanan et al., 1994). He demonstrated previously that fetuses with an abdominal circumference greater than the 75th percentile had a 42% risk of large-for-gestational-age (LGA) babies compared to only 14% in those who did not demonstrate this accumulation of abdominal subcutaneous fat. He randomised 59 GDM women to continue diet vs. beginning on insulin in spite of normal maternal target glucoses. He was able to demonstrate that GDM women who received insulin had lower maternal glucoses levels, and insulin therapy decreased the LGA rate from 45% to 13% compared to women continued on diet alone. This was one of the first studies to suggest that using fetal criteria to direct metabolic management may be more effective than using maternal glucoses criteria alone. In one large European diabetes in pregnancy clinic, amniotic fluid insulin levels are thought to be the best predictor of macrosomia, and decisions about treatment...
therapy in the mother are based on the presence of fetal hyperinsulinaemia (Haeuksler et al., 1998).

Postpartum prevention of Type 2 diabetes in GDM women
Women with a history of GDM should have their glycaemic status reassessed at 6 weeks postpartum. Hyperglycaemia generally resolves in the majority, but up to 10% of patients will fulfill criteria for Type 2 DM and another ~15% will demonstrate impaired glucose tolerance (Conway and Langer, 1999). Women with IGT are the most potent predictor of the development of Type 2 DM in women with a history of GDM (Kjos et al., 1995). Intensified efforts promoting diet, exercise, and weight loss should be instituted in these patients. Non-diabetic women with a history of GDM should have annual measurements of their fasting glucose. The TRIPOD study demonstrated that the use of a thiazolidinedione postpartum in women with a history of GDM and persistent IGT decreased the development of Type 2 DM (Buchanan et al., 2002). The rate of Type 2 DM in the 133 women randomised to Troglitazone was 5.4% vs. 12.1% in the 133 women randomised to placebo at a median follow-up of 30 months (Buchanan et al., 2002). The protection from diabetes was related closely to the degree of reduction of insulin secretion 3 months after randomisation and persisted 8 months after the medication was stopped. Metformin has not been studied in this particular subgroup but has been shown to be effective, as was diet and exercise, in another population with IGT at risk for Type 2 DM in the Diabetes Prevention Study (Diabetes Prevention Program Research Group, 2002). These interventions require intense study for the primary prevention of Type 2 DM in this extremely high-risk group. Breastfeeding should also be encouraged due to data showing that it appears to lower the incidence of developing Type 2 DM in the mother and also decrease the risk of developing infant obesity and impaired glucose tolerance in the offspring (Dabelea et al., 2000).

Future directions in research and maternal–fetal management of GDM
One of the greatest challenges we may face is the growing number of women developing gestational diabetes as the obesity epidemic escalates. We must find more effective ways of combining maternal and fetal criteria to dictate the aggressiveness of therapy, given that using maternal criteria alone to direct therapy has been disappointing in decreasing macrosomia. Furthermore, we need to understand the insulin signalling abnormalities that persist in women with a history of gestational diabetes who have impaired glucose tolerance postpartum in order to direct our preventive therapies optimally. The increasing development of GDM and Type 2 DM in the mother and glucose intolerance in the offspring set the stage for a perpetuating cycle that must be addressed aggressively with effective primary prevention strategies and more effective antepartum interventions. Such observations refuel the debate on the significance of GDM. If in-utero imprinting in GDM is true than perhaps...

‘In my beginning, is my end.’
T.S. Eliot, *Four Quarters, The Dry Salvages*

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