Gestational Diabetes and Insulin Resistance: Role in Short- and Long-Term Implications for Mother and Fetus

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ABSTRACT Gestational diabetes and obesity are the common metabolic abnormalities occurring during pregnancy. Decreased maternal pregravid insulin sensitivity (insulin resistance) coupled with an inadequate insulin response are the pathophysiological mechanisms underlying the development of gestational diabetes. Insulin-regulated carbohydrate, lipid and protein metabolism are all affected to a variable degree. Decreased maternal insulin sensitivity in women with gestational diabetes may increase nutrient availability to the fetus, possibly accounting for an increased risk of fetal overgrowth and adiposity. Epidemiological studies from Europe show an increased risk of the insulin resistance syndrome in adults who were low birth weight at delivery. However, in the United States over the past 20 y there has been a significant 33% increase in the incidence of type 2 diabetes, which has been associated with a parallel increase in obesity. All age groups have been affected but the most dramatic increases have occurred in adolescents. The relationship between decreased maternal insulin sensitivity and fetal overgrowth particularly in obese women and women with gestational diabetes may help explain the increased incidence of adolescent obesity and related glucose intolerance in the offspring of these women. In this review, we address 1) the pathophysiology of gestational diabetes, 2) the changes in maternal insulin sensitivity during pregnancy that effect maternal accretion of adipose tissue and energy expenditure, 3) the influence of maternal metabolic environment on fetal growth, 4) the life-long effect of being born at either extreme of the birth weight continuum and 5) micronutrients and decreased insulin sensitivity during pregnancy. J. Nutr. 133: 1674S–1683S, 2003.

KEY WORDS: • insulin resistance • gestational diabetes

In the United States 135,000 women per year develop gestational diabetes (1). The prevalence of gestational diabetes increased in developed countries from 2.9% to 8.8% over 20 y, particularly in populations immigrating from less-developed areas (2). Furthermore, there is a significant risk of adolescent obesity and type 2 diabetes in the offspring of these women (3,4). Given the tremendous increase in the prevalence of adolescent obesity and type 2 diabetes in the United States over the past 10 y, the long-term implications for developing counties are important. As developing areas strive to meet the nutritional demands of women of reproductive age, there is the potential that the converse problems of macrosomia leading to adolescent type 2 diabetes and obesity may emerge. In this review, we concentrate on the role of insulin resistance in the pathophysiology of gestational diabetes and the implications for mother and fetus.

Gestational diabetes is carbohydrate intolerance of varied severity that begins or is first recognized during pregnancy (5). Insulin may be used for treatment and the condition may persist after pregnancy. Unrecognized glucose intolerance may have antedated the pregnancy. The underlying pathophysiology of gestational diabetes is a function of decreased maternal insulin sensitivity or increased insulin resistance. We define insulin resistance as the inability of a defined concentration of insulin to effect a predictable biological response of nutrient metabolism at the level of the target tissue. Insulin resistance as it relates to glucose metabolism results in decreased glucose uptake in skeletal muscle, white adipose tissue and liver as well as decreased suppression of endogenous (primarily hepatic) glucose production. The manifestation of these abnormalities of glucose metabolism become clinically evident when beta cell response is inadequate. Although we primarily relate insulin resistance to glucose metabolism, other nutrients are also...

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involved. Insulin resistance results in the inability of insulin to suppress lipolysis, and increased insulin resistance results in a decreased ability of insulin to suppress amino acid turnover. Additionally, in women with gestational diabetes, alterations in nutrient metabolism existed before gestation.

**Pathophysiology of gestational diabetes**

**Glucose metabolism.** The pathophysiology of gestational diabetes involves abnormalities of insulin-sensitive tissue. Beta cell sensing of glucose is also abnormal and is manifested as an inadequate insulin response for a given degree of glycemia. Earlier studies reported that the incidence of islet cell antibodies in women with gestational diabetes as measured by immunofluorescence techniques is between 10% and 35% (6). Recent studies using specific monoclonal antibodies, however, have found a lower incidence on the order of 1–2% (7), suggesting a low risk of type 1 diabetes in women with gestational diabetes. Postpartum studies of women with gestational diabetes have demonstrated defects in insulin secretory response and decreased insulin sensitivity (8), indicating typical type 2 abnormalities in glucose metabolism. The alterations in insulin secretory response and insulin resistance in women with a previous history of gestational diabetes as compared with a weight-matched control group may differ depending on whether the women with previous gestational diabetes are lean or obese. Thus in women with gestational diabetes, the metabolic stress of pregnancy may unmask a genetic susceptibility to type 2 diabetes.

Significant alterations in glucose metabolism occur in women who develop gestational diabetes relative to pregnant women with normal glucose tolerance. Decreased insulin response to a glucose challenge was demonstrated by Xiang et al. (9) in women with gestational diabetes in late gestation. In longitudinal studies of both lean and obese women with gestational diabetes, Catalano et al. (10) showed a progressive decrease in first-phase insulin response in late gestation in lean women compared with a weight-matched control group (Fig. 1). In contrast, in obese women developing gestational diabetes, first-phase insulin response did not change but second-phase insulin response significantly increased to an intravenous glucose challenge compared with a weight-matched control group (Fig. 2) (11). These differences in insulin response may be related to the ethnicity of the study groups. The studies by Xiang et al. focused on Latina women whereas our evaluation was of a white study group. However, we believe that the primary reason for the differences in insulin response is the presence or absence of obesity in our study groups. Although there is an increase in the metabolic clearance rate of insulin with advancing gestation, no evidence exists for a difference in insulin clearance between women with normal glucose tolerance and gestational diabetes (11).

Basal glucose concentrations decrease with advancing gestation in women developing gestational diabetes. In late gestation, hepatic glucose production was reported by Xiang et al. (9) to be increased in women with gestational diabetes in comparison with a control group whereas no difference was noted in either fasting glucose concentration or hepatic glucose production in the longitudinal studies of Catalano et al. (10,11). These differences may be population specific and related to the degree of glucose intolerance. However, to date all reports indicate that in late gestation, women with gestational diabetes have increased fasting insulin concentrations (Fig. 3) and less suppression of hepatic glucose production during insulin infusion, thereby indicating decreased hepatic insulin sensitivity in women with gestational diabetes compared with a weight-matched control group (9–11). In the studies of Xiang et al. (9), there was a significant correlation between fasting free fatty acids and hepatic glucose production, suggesting that free fatty acids may further contribute to hepatic insulin resistance.

Women with gestational diabetes have decreased insulin sensitivity in comparison with weight-matched control groups. Ryan et al. (13) were the first to report a 40% decrease in insulin sensitivity in women with gestational diabetes in comparison with a pregnant control group in late pregnancy using a euglycemic clamp. Xiang et al. (9), reported that women with gestational diabetes, who had normal glucose tolerance within 6 mo of delivery, had significantly decreased insulin sensitivity as estimated by the glucose clearance rate during a hyperinsulinemic-euglycemic clamp when compared with a matched control group (11). Similar techniques described the longitudinal changes in insulin sensitivity in both lean and obese women developing gestational diabetes in comparison with a matched control group. Women developing gestational diabetes had lower pregravid insulin sensitivity than did the matched control group (Fig. 4). The differences in insulin sensitivity between the groups were greatest before and during early gestation and were less pronounced but still significant by late gestation. Of note, in Figure 4, there was an increase in insulin sensitivity from the time before conception through early pregnancy, particularly in women with the lowest pregravid insulin sensitivity.
Studies in human skeletal muscle and adipose tissue have demonstrated that postreceptor defects in the insulin signaling cascade are related to decreased insulin sensitivity in pregnancy. Garvey et al. (14) were the first to demonstrate that there were no significant differences in the concentration of the glucose transporter (GLUT 4) responsible for insulin action in skeletal muscle of pregnant compared with nonpregnant women despite reduced insulin-stimulated glucose transport. On the basis of studies by Friedman et al. (15) in pregnant women with normal glucose tolerance and gestational diabetes as well as a nonpregnant control group, several defects in the insulin signaling cascade were characterized in late pregnancy. Additional abnormalities were observed in women with gestational diabetes. Pregnant women appeared to have a decrease in insulin receptor substrate-1 expression; its down-regulation closely parallels the decreased ability of insulin to induce additional steps in the insulin signaling cascade. This results in a decrease in insulin-stimulated 2-deoxyglucose uptake in vitro. In addition to the above mechanisms, women with gestational diabetes demonstrate a distinct decrease in the ability of the insulin receptor beta subunit to undergo tyrosine phosphorylation. This additional defect in the insulin signaling cascade results in a 25% lower glucose transport activity in muscle compared with that in nondiabetic pregnant women.

**Amino acid metabolism**

In addition to glucose, which is the primary energy source of fetoplacental tissues, accretion of protein is essential for fetal growth. Nitrogen retention is increased in pregnancy in both maternal and fetal compartments. It is estimated that there is a 500-g increase in protein accretion by about 30 wk (16). A significant decrease occurs in most fasting maternal amino acid concentrations in early pregnancy before the accretion of significant maternal or fetal tissue (17). These anticipatory changes in fasting amino acid metabolism occur after a shorter period of fasting in comparison with nonpregnant women. Maternal amino acid concentrations were significantly decreased in mothers of small-for-gestational-age neonates compared with maternal concentrations in appropriate-size neonates (18).

Protein turnover (i.e., protein synthesis and degradation), is measured with stable isotopes techniques using specific amino
Acids. Based on a review of various studies, Duggleby and Jackson (19) estimated that during pregnancy, protein synthesis is similar to that for nonpregnant women in the first trimester. However, a 15% increase occurs during the second trimester and a further increase of about 25% occurs in the third trimester. Additionally, there are marked interindividual differences at each time that have a strong relationship with fetal growth; mothers who had increased protein turnover in midpregnancy had infants who had increased lean body mass after adjustment for significant covariables (20).

Amino acids can be used either for protein accrual or oxidized as an energy source. Urea synthesis has been estimated with the use of stable isotopes in a number of studies. In general, there is a modest shift in oxidation in early pregnancy with an accrual of amino acids for protein synthesis in late gestation (20). Kalhan et al. (21) reported that there are significant pregnancy-related adaptations in maternal protein metabolism early in gestation before any significant increase in fetal protein accretion. Preliminary studies by Catalano et al. (22) reported that decreased insulin sensitivity manifested by a decreased suppression of leucine turnover occurs during insulin infusion in late gestation in all pregnant women. Furthermore, there is evidence for an increase in basal leucine turnover in women with gestational diabetes compared with a matched control group. Whether these decreases in amino acid insulin sensitivity are related to decreased whole-body or liver protein synthesis or increased breakdown are not known.

**Lipid metabolism**

Although ample literature exists on the changes in glucose metabolism during gestation, data on the alterations in lipid metabolism are meager. Darmady and Postle (23) measured serum cholesterol and triacylglycerol before, during and after pregnancy in 34 normal women. Both cholesterol and triacylglycerol decreased at approximately 7 wk gestation and then increased progressively until term. Serum triacylglycerol decreased postpartum. The decrease was more rapid in women who breast-fed than in those who bottle fed their infants.

The increase in maternal free fatty acids in late gestation has been hypothesized to be a mechanism related to the decrease in maternal glucose insulin sensitivity in late pregnancy. Free fatty acids have also been associated with fetal overgrowth particularly of adipose tissue. There is a significant difference in the arteriovenous free fatty acid concentration at birth much as there is with arteriovenous glucose concentration. Knopp et al. (24) reported that neonatal birth weight was positively correlated with concentrations of triacylglycerol and free fatty acid, which readily cross the placenta in late pregnancy. Similar conclusions were reached by Ogburn et al. (25) who using a pregnant ewe model showed that increased fetal insulin concentrations suppress fatty acid concentrations, inhibit lipolysis and result in increased fat deposition. Kleigman et al. (26) reported that infants of obese women not only had increased birth weight and skinfold measurements but increased serum free fatty acids compared with infants from lean women.

In women with gestational diabetes, Knopp et al. (27) reported that there is an associated increase in triacylglycerol and decrease in high-density lipoprotein concentration. However, Montelongo et al. (28) reported little change in free fatty acid concentrations through all three trimesters after a 12-h fast. Recently, Koukkou et al. (29) reported an increase in total triacylglycerol but a lower low-density lipoprotein cholesterol in women with gestational diabetes. Hyperinsulinemic-euglycemic clamp studies in pregnant women with normal glucose tolerance (30) and gestational diabetes (31) showed that there was a decreased ability of insulin to suppress free fatty acids with advancing gestation. Insulin’s ability to suppress plasma free fatty acid was less in women with gestational diabetes than in women with normal glucose tolerance (31).

Taken together these studies demonstrate that insulin sensitivity to nutrients decreases in all women with advancing gestation. These decreases in insulin sensitivity are further enhanced by the presence of decreased pregravid maternal insulin sensitivity, which becomes manifest in later pregnancy as gestational diabetes. The result of the decreases in insulin sensitivity is greater nutrient availability and higher ambient insulin concentrations for the developing fetoplacental unit, which may eventually result in fetal overgrowth.

**Short- and long-term implications of decreased insulin sensitivity**

**Fetal and neonatal implications.** At birth the human fetus has a significantly greater amount of body fat, approximately 12%–16%, than do other mammalian species. For example, mice, rats and lambs, which are commonly used in perinatal metabolic studies, have about 1–3% body fat at birth.

**Influence of parental anthropometrics.** Various demographic parental anthropometric factors have been correlated with fetal growth (32–33). Many of these variables (e.g., maternal prepregnancy weight or weight gain during pregnancy) have commonly been thought to be excellent predictors of birth weight. Although statistically significant, these factors explain only approximately 20–30% of the variance in birth weight.

Maternal nutrition is obviously an important factor in determining fetal growth. Based on the data from the Dutch famine of 1944–1945 (34), the level of energy intake associated with nutritional deprivation and impaired fetal growth is approximately <1500 kcal/d. Deprivation in early gestation is associated with a higher rate of prematurity and very low birth weight whereas deprivation in late gestation is associated with 9% lower fetal weight but not length (34). In contrast, Ravelli et al. (35) reported in the same population, that neonates exposed to famine in early pregnancy were heavier and longer than unexposed children at birth. The size of the head as well as their placentas, however, were smaller. The infants of the women exposed to the famine in late pregnancy were on average lighter, shorter and thinner than infants of women not exposed to famine. Of interest, mothers exposed to famine in early pregnancy gained more weight than women not exposed to the famine. In follow-up studies at age 50 y, female infants exposed to the famine in early pregnancy had increased body weight, body mass index and waist circumference (36). We speculate that the increase in maternal weight gain in pregnancy and female infant weight gain into adult life may have resulted from increased maternal nutrient intake in mid to late gestation possibly resulting in increased fetal adiposity relative to a control group not exposed to famine. Nutritional supplementation can improve birth weight. Based on studies in Guatemala (37), the type of supplementation (i.e., protein or carbohydrate) may not make a difference in the increase in birth weight if minimal protein requirements are achieved. Prentice et al. (38) observed a mean increase in birth weight of 225 ± 56 g in women in The Gambia who received a dietary supplement (430 kcal/d). However, this increase only occurred when food shortages and increased work load resulted in a negative energy balance.

Maternal anthropometric variables are important factors related to fetal growth. Maternal prepregnant weight is a strong predictor of birth weight (39). Maternal height is also associated with an increase in birth weight, but when maternal...
height is adjusted for weight, there is no longer a significant correlation between maternal height and birth weight (40). Maternal weight gain during gestation is also correlated with birth weight: \( r = 0.26 \) in nulliparous women and \( r = 0.16 \) in multiparous women (40). The interaction of maternal pregravid weight and weight gain was examined by Abrams and Laros (41). They reported that there was a progressively stronger correlation between maternal weight gain and birth weight in women who were moderately overweight, had ideal body weight and were underweight. In women >135% of ideal weight for height before conception, there was no correlation between weight gain during pregnancy and birth weight. The mean birth weight of the infants of the very obese women was the greatest in their study population. Parity was shown to have a positive correlation with birth weight. McKeown and Gibson (42) reported that when maternal age was adjusted for parity, no consistent correlation was seen between maternal age and birth weight. Parity was shown by Thompson et al. (33) to be associated with a 100–150-g increase in birth weight in subsequent pregnancies. However, the additional effect of parity on birth weight is diminished with increasing parity.

Relative to maternal anthropometric factors, maternal anthropometric factors have a limited effect on fetal birth weight. Morton (43) reported that in half-siblings where the mother was the common parent, the correlation in birth weight between the half-siblings was \( r = 0.58 \). In contrast, the correlation of birth weight in half-siblings where the father is the common parent was only \( r = 0.10 \). Crossbreeding studies support these findings. In the studies by Walton and Hammond (44), Shetland ponies and Shire horses were crossbred. The size of the foals was roughly the same size as the maternal pure breed. A recent study by Klebanoff et al. (45) reported that paternal birth weight, adult height and adult weight explained about 3% of the variance in infant birth weight versus 9% for the corresponding maternal factors.

**Influence of metabolic environment: role of insulin sensitivity.** In an effort to improve our understanding of factors affecting fetal growth, we conducted a series of studies in which we estimated neonatal body composition. As noted by Sparks (46), genetic factors may have a stronger relationship with fat-free body mass whereas in utero environment may correlate better with fetal fat mass. In a series of metabolic studies we used anthropometric methods to estimate body composition in 183 neonates (47). Fat-free mass, which comprised 86% of mean birth weight, accounted for 83% of the variance in birth weight; fat mass, which comprised only 14% of birth weight, accounted for 46% of the variance in birth weight. Male infants also had significantly greater fat-free mass but not fat mass than did female infants (48). Using independent variables such as maternal height, pregravid weight, weight gain during pregnancy, parity, paternal height and weight, neonatal sex and gestational age, we accounted for 29% of the variance in birth weight, 30% of the variance in fat-free mass and 17% of the variance in fat mass (Table 1) (48). Including estimates of maternal insulin sensitivity in 16 lean subjects, increased our ability to explain approximately 50% of the variance in body composition (Table 2) (49). The strongest correlation with fetal fat accretion was pregravid maternal insulin sensitivity (\( R^2 = 0.15 \)). We speculate that because obese women are in general less insulin sensitive than a normal-weight population, they have the greatest risk of having a large baby. Kleigman et al. (26) reported that maternal obesity was a twofold (15% vs. 8%) greater risk in a woman having a large infant than in women with diabetes. Studies by Caruso et al. (50) corroborated these findings by looking at the opposite end of the birth-weight spectrum. They reported that women with unexplained fetal growth restriction had greater insulin sensitivity than did a control group of women whose infants were of appropriate weight for gestational age. Therefore, increased maternal insulin sensitivity may decrease nutrient availability to the fetus, resulting in undergrowth.

**Life-long effect of extreme birth weights.** From studies by Hales et al. (51), low birth weight may affect the life-long development of the organism. Environmental stress in utero, particularly at critical periods of development, may have long-term effects on metabolic function. In studies of the Hertfordshire population, low birth weight was a significant risk

### Table 1

<table>
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<th>Dependent and independent variables</th>
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<th>( \Delta R^2 )</th>
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### Table 2

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Reprinted with permission from reference 48.
factor for the development of glucose intolerance at age 64. The proportion of men with either diabetes or impaired glucose tolerance fell inversely with increasing birth weight and weight at age 1. Obesity was not a hallmark of their population although it was an independent risk factor. The authors hypothesized that beta cell development and function may be impaired because of the nutritional deprivation in utero and through age 1 y that resulted in adverse stimuli. An increased risk of the features associated with metabolic syndrome (e.g., hypertension and hyperlipidemia in their low-birth-weight cohort) was also noted.

From 1990 to 1998 in the United States, the prevalence of type 2 diabetes increased 33%, including in children (52). The prevalence was strongly correlated with obesity. Eighty–fifty percent of children diagnosed with type 2 diabetes are obese (53). Additionally, in a recent study by Sinha et al. (54), impaired glucose tolerance was diagnosed in 25% of obese children (ages 4–10 y) and 21% of obese adolescents (ages 11–18 y). In this study impaired glucose tolerance was associated with insulin resistance whereas beta cell function was relatively preserved.

Infants of women with gestational diabetes have increased body fat compared with weight-matched infants of control women (55). The increased birth weight of these infants then tends to normalize by age 1 y before increasing again during early childhood. Silverman et al. (3) reported a strong correlation between amniotic fluid insulin levels and increased body mass index in adolescents aged 14–17 y, indicating an association between islet cell activation in utero and the development of childhood obesity. This obesity present in childhood then predisposes to obesity in the adult. Pettitt et al. (4) showed that infants born to Pima Indian women with impaired glucose tolerance were more obese as children than infants of women with normal glucose tolerance even when they developed diabetes in later life. Additionally, maternal family history was shown to have an increased relative risk of 2.51 (95% confidence interval: 1.55–4.17) compared with a nonsignificant paternal family history relative risk of 1.41 (95% confidence interval 0.55–3.05) (56). These risks were adjusted for glucose disappearance rate from an intravenous glucose tolerance test, fasting glucose, obesity, physical fitness, triacylglycerol concentrations and age. The data suggest that both in utero maternal metabolic factors as well genetic factors participate in the subsequent development of type 2 diabetes and obesity.

In summary, from available data we are only able to explain a relatively small amount of the variance in fetal growth using parental demographic and anthropometric factors. However, when we incorporate measures of maternal insulin sensitivity, we are able to explain approximately twice the variance in fetal growth, in particular accretion of adipose tissue. Decreased maternal insulin sensitivity before conception was found to have the strongest correlation with fetal fat mass at term. These data support the observation that decreased maternal insulin sensitivity, as observed in obese women and women with gestational diabetes, is associated with fetal overgrowth, in particular of adipose tissue, which may be a long-term risk factor for obesity and glucose intolerance in these children.

**Maternal implications**

Estimates of the energy cost of pregnancy range from a cost of 80,000 kcal to a net savings of 10,000 kcal (57). As a result, the recommendations for nutritional intake in pregnancy are diverse and depend on the population being evaluated. Furthermore, on the basis of more recent data, recommendations for populations within a population may be more diverse than previously believed, making general guidelines for nutritional intake difficult (58).

The theoretical energy cost of pregnancy was estimated by Hytten and Leitch (15). The additional energy cost of pregnancy consisted of the additional maternal and feto-placental tissue accrued during pregnancy and the additional running cost of pregnancy, for example, increased cardiac output. In Hytten and Leitch’s model the greatest increases in maternal energy expenditure occur between 10 and 30 wk gestation, primarily because of maternal accretion of adipose tissue. However, the mean increases in maternal adipose tissue vary considerably among various ethnic groups. Forsum et al. (59) reported a mean increase of >5 kg of adipose tissue in Swedish women whereas Lawrence et al. (60) found no increase in adipose tissue stores in women from The Gambia with their usual nutritional intake. Basal metabolic rate accounts for 60–70% of total energy expenditure in individuals not engaged in competitive physical activity and correlates well with total energy expenditure. With the changes in maternal accretion of adipose tissue, there are wide variations in the change in maternal basal metabolic rate during gestation. The cumulative changes in basal metabolic rate range from a high of 52,000 kcal in Swedish women (61) to a net savings of 10,700 kcal in women from The Gambia (60) without nutritional supplementation. The mean increase in basal metabolic rate in Western women averages approximately 20% (62). However, the coefficient of variation in basal metabolic rate in these populations during gestation ranges from 93% in women from the United Kingdom (58) to >200% in Swedish women (61). When assessing energy intake in relation to energy expenditure, however, estimated energy intake remains significantly lower than the estimates of total energy expenditure. These discrepancies have usually been explained by factors such as increased metabolic efficiency during gestation, decreased maternal activity and unreliable assessment of food intake (63,64).

Data in nonpregnant subjects may help explain some of the wide variations in metabolic variables measured during human gestation. Swinburn et al. (65) reported that Pima Indians with decreased insulin sensitivity gained less weight than did insulin-sensitive subjects (3.1 vs. 7.6 kg) over 4 y. Furthermore, the percent weight change per year was highly correlated with glucose disposal. Catalano et al. (66) conducted a study of the changes in maternal body fat and energy expenditure in women with normal glucose tolerance and gestational diabetes in relation to insulin sensitivity in early pregnancy. Women with gestational diabetes had decreased glucose insulin sensitivity before conception and had significantly smaller increases in body fat and energy expenditure than did women with normal glucose tolerance. A significant inverse correlation occurred between the changes in fat accretion and insulin sensitivity: women with decreased pregravid insulin sensitivity (i.e., obesity and gestational diabetes) had less accretion of body fat than did women with increased pregravid insulin sensitivity. These results are consistent with a previous report showing that weight gain in lean women with gestational diabetes was 2.5 kg less than in a matched control group (67).

Similarly, an inverse relationship was noted between the changes in total energy expenditure and insulin sensitivity (66). Women with decreased pregravid insulin sensitivity had little or no increase in energy expenditure and in some cases a decrease in energy expenditure compared with pregravid measurements. In contrast, women who were more insulin sensitive had greater increases in energy expenditure in early pregnancy.

To place these data in perspective, a closer look at the data of Lawrence et al. (60) in The Gambia is necessary. In this study
some women had their basic 1500-kcal diet supplemented by 400 kcal/d. In women whose diets were not supplemented, maternal body fat did not increase and basal metabolic rate actually decreased during the first 30 wk gestation. However, when these diets were supplemented gain of 2 kg fat, and although basal metabolic rate decreased in early pregnancy, it returned to pregravid levels by 20 wk gestation. As a result of the changes in basal metabolic rate and body composition, there was a saving of 11,700 kcal in the group not supplemented and a cost of 27,500 kcal in the supplemented group. Hence, if we assume that women in The Gambia were genetically insulin resistant, then the energy supplementation may have resulted in a change from net savings of energy to net cost of energy. Additionally, there was a mean increase of 225 ± 56 g in the offspring of the women whose diets were supplemented. However, the increase in birth weight only occurred during the wet season when the women were in negative energy balance because of food shortages and an increased work load (38). We speculate that the increased fetal growth may have resulted primarily in accretion of adipose tissue.

Women with gestational diabetes are at an increased risk of developing type 2 diabetes. The original studies of O'Sullivan (68) show that the 15-y prevalence of type 2 diabetes in women with a history of gestational diabetes was approximately 60% in obese women during pregnancy and 30% in lean women at the time of diagnosis. Subsequent studies supported these original findings. The greatest risk factor for early-onset type 2 diabetes after pregnancy was early gestational age at the time of diagnosis and elevated fasting glucose (69). The greatest long-term risk factor was maternal obesity (70).

In summary, the results of these studies show that there is a relationship between the changes in maternal insulin sensitivity and changes in accretion of adipose tissue and energy expenditure in early gestation. The ability of women with decreased pregravid insulin sensitivity to conserve energy expenditure and accretion of body fat and make available sufficient nutrients to produce a healthy fetus is a reproductive advantage when availability of food is marginal. These data support the thrifty gene hypothesis that decreased maternal insulin sensitivity may have a reproductive metabolic advantage in times of nutritional dearth. In contrast, decreased maternal insulin sensitivity before conception in an environment where food is plentiful and a sedentary lifestyle is more common may manifest itself as gestational diabetes during pregnancy. This may then increase the long-term risk for both diabetes and obesity in the woman and her offspring.

Micronutrients and decreased insulin sensitivity during pregnancy

If decreased maternal insulin sensitivity during gestation potentially results in adverse maternal and fetal consequences, can any dietary micronutrient interventions improve maternal insulin sensitivity? The metabolism of zinc, magnesium and chromium may be altered in women with gestational diabetes. Increases in urinary excretion and lower circulating levels of these nutrients have been reported in diabetic women. It is unclear, however, whether these shifts affect fetal growth or maternal health.

Zinc. Studies of zinc depletion in experimental animals show that zinc is required for normal glucose metabolism. The incorporation of [14C]glucose into fatty acids in epididymal fat pads is reduced in zinc-deficient rats. Recent research by Tang and Shay (71) provides a mechanism for this observation. A correlation had been shown between zinc and the degree of glycosuria and serum hemoglobin A1c concentrations (72). Serum zinc concentrations may have an insulin-like effect on glucose transport into adipocytes. Zinc potentiates insulin-induced glucose transport into cells by influencing the insulin signaling pathway. This may explain why glucose use is reduced and lipolysis is enhanced in zinc deficiency (71). Experimental zinc depletion confirms that zinc depletion also alters glucose metabolism in humans. Men with zinc depletion exhibited a rise in plasma glucose concentrations and a decline in respiratory quotient (73). Because pregnancy creates a state of insulin resistance and hyperglycemia, mothers in a marginal state of zinc nutrition may be at risk for developing gestational diabetes.

Diabetes per se also appears to alter zinc metabolism. Urinary zinc excretion is elevated in diabetic patients compared with control subjects (74,75). This increase is associated with urinary protein losses. Urinary zinc was not associated with the excretion of any amino acid, urea or ammonia. Possibly, glycosylated amino acids or peptides chelated with zinc contributed to the increased urinary zinc losses. A decline in serum zinc may also be related to diabetic control (76). Zinc originating from bone loss and exogenous insulin accounted for a small part of the hyperzincemia. Other homeostatic adjustments must have occurred. Rats made diabetic by the administration of streptozotocin did not have an increase in zinc absorption but the amount of zinc excreted into the intestine was reduced (77).

This decreased endogenous loss of zinc into the intestine may be a homeostatic response to the increased urinary excretion of endogenous zinc in diabetic patients.

The role of zinc in gestational diabetes is not well established. Studies in diabetic pregnant rats suggest that zinc transport to the fetus is reduced either because of a decrease in placental transport or altered maternal or fetal zinc-binding ligands (78). In humans no differences in serum zinc were observed between insulin-requiring diabetic women and control pregnant women if the diabetic women were maintaining careful control (79). Further research is needed to establish the effects of marginal zinc status on glucose homeostasis in women during pregnancy.

Magnesium. Type 1 diabetes is associated with increased urinary losses of magnesium (80). Serum magnesium levels also were lower in women with type 1 diabetes compared with control women (80). Serum magnesium concentrations are inversely related to glycosylated hemoglobin concentrations and glucosuria. The increased urinary losses may be related to hyperfiltration in combination with impaired tubular reabsorption. A reduction in serum magnesium may reflect depressed tissue magnesium levels. Lower levels of striated muscle magnesium were measured in patients with diabetes requiring insulin (81).

Decreases in serum magnesium and increased urinary losses of magnesium were reported in type 1 diabetes and gestational diabetes (79). These lower levels persisted after good glycemic control was achieved. The fall in serum magnesium during pregnancy in both healthy and diabetic women is probably due partly to the decline in serum albumin concentrations because about one-third of serum magnesium is transported by albumin. Magnesium depends on insulin for entry into cells. More intensive treatment with insulin during pregnancy in women with gestational diabetes may lead to a further decline in circulating magnesium. No functional consequences of this lower level of magnesium during gestation in diabetic women have been reported.

Chromium. Chromium is thought to play a role in the function of insulin. Chromium was identified as an essential nutrient because it restored glucose tolerance in rats fed low-chromium diets (82). However, a specific function for chro-
 chromium plays a role in the pathogenesis of diabetes in humans. Several investigators have reported that hair chromium concentrations decline during pregnancy (82,83) and the concentration of hair chromium was markedly reduced in women who had repeated pregnancies within 4 y (84). To test the effect of chromium supplementation on glucose tolerance in pregnancy, Jovanovic-Peterson and Peterson (82) randomly assigned 24 women with gestational diabetes to a chromium supplementation (4 μg/[kg-d]−1) or placebo group. Subjects given supplemental chromium had lower fasting and peak blood glucose levels. However, supplemental chromium did not lower blood glucose concentrations in women with severe glucose intolerance enough to eliminate the need to give insulin. Presently, chromium is not an accepted treatment for gestational diabetes nor is there sufficient evidence that poor chromium status increases the risk for gestational diabetes.

Pregestational diabetes: maternal and fetal risks

Before the increases in type 2 diabetes in the United States over the past 10–20 y, most women with pregestational diabetes had type 1 rather than type 2 diabetes. Women with pregestational diabetes, whether type 1 or type 2, undergo changes in glucose metabolism that are similar when compared with women with normal glucose metabolism or gestational diabetes. In women with well-controlled type 1 diabetes, there may be a 10–15% decrease in insulin requirements from 10 to 17 wk gestation and a 50% increase from 17 wk until term compared with pregravid requirements (85).

Women with pregestational diabetes, whether type 1 or type 2, are at increased risk for having offspring with major organ structural anomalies (86). The risk of congenital anomalies is related to the degree of glucose control during organogenesis (i.e., the first 6–8 wk gestation). In contrast, women with normal pregravid glucose tolerance who develop gestational diabetes in late gestation have no increased risk of fetal congenital anomalies beyond the population risk for women with normal glucose metabolism.

Relative to fetal growth, women with pregestational diabetes may have an increased risk of fetal growth restriction as compared with women with normal glucose tolerance or gestational diabetes. The risk of fetal growth restriction may be related to the increased incidence of comorbidities in these women such as chronic hypertension or diabetic nephropathy. These comorbidities may also increase the risk of preterm delivery relative to a control group of women with gestational diabetes because of the increased incidence of preeclampsia in these women (87). The long-term risks of obesity and risk of type 2 diabetes in the offspring of these women have been less well examined, although we speculate that they may mirror the findings in the population of women with gestational diabetes.

Summary

The development of insulin resistance in late gestation is a process common to all human pregnancies. The development of maternal insulin resistance is associated with accretion of maternal adipose tissue in early pregnancy and increased fetoplacental nutrient availability in late gestation, when 70% of fetal growth occurs. In women who develop gestational diabetes, insulin resistance is increased before conception, often in association with maternal obesity and increased risk of fetal macrosomia or overgrowth. The macrosomic infants of these women have an increased risk for the development of adolescent obesity and type 2 diabetes. Efforts are urgently needed to reverse these trends in the developed areas of the world, in particular the United States, and prevent the problem in the developing world. Increased maternal insulin resistance may have a reproductive advantage when there is a dearth of food and excessive maternal work but may develop with the incorporation of Western diets and decreased physical activity. To date, the primary means to prevent the development of insulin resistance are lifestyle measures of diet, activity and avoidance of obesity. The potential role of micronutrients to improve insulin resistance in women of reproductive age is a potential avenue to explore but needs further evaluation. In the interim, it appears prudent to stress the importance of lifestyle measures in order to prevent the potential long-term implications of altered fetal growth.

LITERATURE CITED


