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MATERNAL OBESITY, METABOLISM, AND PREGNANCY OUTCOMES

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■ **Abstract** About one third of all pregnant women in the United States are obese. Maternal obesity at conception alters gestational metabolic adjustments and affects placental, embryonic, and fetal growth and development. Neural tube defects and other developmental anomalies are more common in infants born to obese women; these defects have been linked to poor glycemic control. Preeclampsia, a gestational disorder occurring more frequently in obese women, appears to be due to a subclinical inflammatory state that impairs early placentation and development of its blood supply. Fetal growth and development during the last half of pregnancy depends on maternal metabolic adjustments dictated by placental hormones and the subsequent oxygen and nutrient supply. Maternal obesity affects these metabolic adjustments as well. Basal metabolic rates are significantly higher in obese women, and maternal fat gain is lower, possibly in response to altered leptin function. The usual increase in insulin resistance seen in late pregnancy is enhanced in obese mothers, causing marked postprandial increases in glucose, lipids, and amino acids and excessive fetal exposure to fuel sources, which in turn increases fetal size, fat stores, and risk for disease postnatally. Impaired glucose tolerance, gestational diabetes, and hyperlipidemia are more common among obese mothers. To date, little attention has been given to the role of diet among obese women in preventing these problems. However, studies of women with impaired glucose tolerance show that replacing refined carbohydrates and saturated fat with complex, low-glycemic carbohydrates and polyunsaturated fatty acids improves metabolic homeostasis and pregnancy outcomes. Thus, current dietary guidelines regarding the amount and type of carbohydrates and fat for nonpregnant women seem appropriate for pregnant women as well.

CONTENTS

INTRODUCTION 272
EMBRYONIC DEVELOPMENT 273
Embryonic and Placental Development 273
Aberrations in Embryonic and Placental Development 274
METABOLISM DURING LATE PREGNANCY 276
Energy Metabolism 276

Fuel Metabolism 279
FETAL GROWTH AND DEVELOPMENT IN LATE PREGNANCY 282
MATERNAL DIET AND PREGNANCY OUTCOMES 283
Dietary Carbohydrate 284
Dietary Fat 284
Diet Recommendations 285
PERSPECTIVES 285

INTRODUCTION

Coincident with the rise in obesity nationwide, the number of women who enter pregnancy obese has reached an all-time high. Based on the prevalence of obesity among women of reproductive age, it appears that at least one third of all pregnant women in the United States are obese. Data from the Centers for Disease Control and Prevention collected in 2000 show that 50% of African American women 40% of Hispanic women, and 30% of white women are obese. Many studies of thin, undernourished women have shown that maternal nutrition at conception influences the metabolic response to pregnancy and fetal growth and development (68). Undernourished women gain less weight, have smaller increases in basal metabolism, and give birth to smaller babies. But the number of studies of pregnancy outcomes among women who enter pregnancy with excessive amounts of fat stores is more limited. As the prevalence of obesity increases, however, it is becoming evident that these women are susceptible to an increased risk of metabolic complications and poor pregnancy outcomes (18, 29, 37). Fetal anomalies as well as deviations in fetal growth rates are more common among obese compared with normal-weight women, suggesting that maternal adiposity affects development during both the embryonic period as well as later in gestation. The intrauterine effects on fetal growth and development may also affect postnatal development of the child, particularly if fetal growth rates are abnormal. Large-for-gestational age (LGA) infants are at increased risk for childhood obesity, which can lead to insulin resistance, diabetes, and hypertension later in life (21). Small-for-gestational age (SGA) infants born to obese women are susceptible to cardiovascular disease and diabetes later in life, particularly if their postnatal catch-up growth produces truncal obesity but the child remains short (89, 92).

Two factors influence fetal growth and development—genetics and the maternal environment (38). Although genetics influences intrauterine growth rates and development of fetal anomalies, it is unlikely that the increased prevalence of fetal complications among obese mothers is due to genetics alone. It is more likely that the environment of obese mothers interacts with genetic factors to induce changes in fetal growth and development. The fetus perceives the maternal environment through signals transmitted by the placenta, such as nutrient transfer, blood hormone, or oxygen levels. The fetus uses this information in two ways: (*a*) to make immediate survival choices and (*b*) to make longer-term adjustments to maximize its advantage postnatally (38). For example, if blood oxygen levels

drop, fetal growth rates slow to conserve oxygen. On the other hand, if the fetus experiences a chronically high blood glucose level, it might anticipate being born into a carbohydrate-rich environment and prepare for that situation by synthesizing and secreting more insulin.

Environmental signals to the fetus from obese mothers that influence fetal development include adjustments in the placental transfer of nutrients (e.g., glucose, fatty acids, amino acids), hormones (e.g., insulin, leptin, adiponectin), and, possibly, inflammatory markers. When these metabolic parameters reach abnormal levels, metabolic complications such as gestational diabetes, pregnancy-induced hypertension, and preeclampsia are diagnosed. Although it is well known that diet influences the development of diabetes and hypertension in nonpregnant adults, the role diet plays in either prevention or management of these disorders among obese pregnant women has received little attention. Consequently, obese women are not given any special prenatal dietary counseling unless they develop gestational diabetes. It is important to know whether adjustments in maternal diet either prior to and/or during gestation improve outcomes among obese women.

This review summarizes the effects of maternal adiposity on placental function and fetal growth and development. Differences in the metabolic adjustments and complications among obese compared with nonobese women are examined and linked, to the extent possible, to pregnancy outcomes. Finally, the potential role of maternal diet, an important aspect of the maternal environment, in influencing gestational metabolic adjustments is discussed.

EMBRYONIC DEVELOPMENT

Embryonic and Placental Development

Human pregnancies are usually divided into two stages of development—embryonic and fetal (38). During the embryonic period, or the first 14 weeks of gestation, gross development of the fetal anatomical features and placental formation occur. The remaining 26 weeks of gestation are devoted to completing fetal growth and development. Prior to implantation, the blastocyst becomes polarized, with one part becoming the embryo and another part forming the placenta. As the cells destined to become the placenta proliferate, they invade the uterine lining and establish contact with maternal blood vessels so that the growing embryo can be nourished (38).

Embryonic and placental development is a very complex process; cells divide and redivide, migrate, differentiate, and undergo apoptosis. Prior to implantation, the embryo is nourished by oviductal and then uterine secretions (13). After implantation and establishment of the placenta, nourishment is provided via exchanges between maternal and fetal circulation. This circulatory exchange is not established until about eight weeks of gestation (13). Thus, the embryo is nourished primarily by maternal uterine gland secretions that are taken up by placental villi.

There is evidence that embryonic development and organogenesis during the first eight weeks is particularly vulnerable to perturbation by free radicals. To reduce the risk of free radical–mediated damage, uterine nutrients are taken up by the placental villi under a low oxygen concentration.

Uterine secretions during the first weeks of gestation are also a rich source of growth factors, such as tumor necrosis factor-a and epidermal growth factor (13). These growth factors influence placental villous development and the subsequent form and function of the mature placenta. This may explain how the maternal environment in early gestation affects pregnancy outcome. Studies in sheep and experimental animals show that poor maternal nutrition during the embryonic period alters health of the offspring. In rats, for example, poor nutrition during embryonic development produces offspring with a high risk of hypertension (38). Sheep fed nutritionally restricted diets during the embryonic period produced offspring with higher amounts of fat than that in lambs born to ewes adequately nourished throughout gestation (75). Evidence is accumulating in humans showing that early maternal undernutrition increases the risk of obesity in the child. For example, children born to women who experienced severe nutritional restriction in early gestation during the five-month Dutch famine in World War II tended to become obese adults (87). Thus, maternal undernutrition early in gestation, when the nutritional demand is low, alters embryonic and placental development in such a way as to influence lifelong health of the offspring. As discussed below, maternal overnutrition also affects the postnatal health of the child.

Aberrations in Embryonic and Placental Development

Infants born to obese women have a higher prevalence of congenital anomalies than do the offspring of normal-weight women, a finding that implies that maternal adiposity alters development during the sensitive embryonic period (18, 29, 37). Adipose tissue is a highly active endocrine organ secreting a number of hormones that alter the circulation of metabolites, cytokines, and growth factors (40, 42). Women who are obese at conception enter the period of embryonic development with metabolic deviations in place that likely contribute to the increased prevalence of congenital malformations.

Data from a large study of 56,857 U.S. women between 1959 and 1966 showed a 1.4-fold increase in major congenital anomalies among infants born to overweight or obese women (64). Case-control studies report that the prevalence of neural tube defects (NTDs) is twice as high among obese women as that in normal-weight or thin women (89). Those studies are subject to the errors of self-reported maternal heights and weights, however. But the relationship persisted in two large cohort studies without the potential flaws in reports of maternal weight (89). Spina bifida is more common than anencephaly, which suggests that these two birth defects have different etiologies (89). NTDs are not the only type of birth defects more common in obese women; other defects include oral clefts, heart anomalies, hydrocephaly, and abdominal wall abnormalities (89).

It is not known why obese women tend to have more birth defects, but evidence is accumulating that the underlying mechanism may be similar to that causing increased anomalies in diabetic mothers. Hyperinsulinemia and poor glycemic control due to insulin resistance are common among the obese, even if they do not have diabetes (40). Studies in diabetic women show that good glucose control in the periconceptional period reduces the risk of birth defects (89). For example, consuming a diet high in sucrose and other high-glycemic foods increased the risk of NTDs approximately twofold among all women (81); the risk was increased to fourfold among women with a body mass index (BMI) >29. The specific mechanism whereby poor glycemic control alters early development is unknown, but studies in experimental animals show that an increase in free radicals alters the expression of transcription factors and contributes to embryopathology (88). Poor folic acid nutrition has also been proposed as a factor increasing the incidence of NTDs in obese women (57, 89). But in a number of epidemiological studies, the relationship between maternal obesity and NTDs persisted after controlling for self-reported folic acid intakes (37). Also, a recent study in Canada showed that the risk of an NTD tended to be more pronounced ($p < 0.09$) in obese women after folic acid supplementation than before (73); the relative risk increased from 1.4 to 2.8. It does not appear, therefore, that poor folic acid nutrition increases the risk of NTDs among obese women. Instead, poor glycemic control seems to be a more likely explanation.

Placental development also appears to be affected by maternal obesity. Delivery of overgrown LGA infants occurs more frequently among obese than normal-weight women (18). Obese women are more likely to have larger placentas as well as bigger babies (94). Recent studies show that a high placental weight relative to birth weight predicts adult-onset diseases such as hypertension (3), coronary heart disease (2), and diabetes (76). Larger placental-to-birth weight ratios are more common in women with high BMIs (56), a finding that implies that an imbalance between placental and birth weight is a risk factor for chronic disease later in life in children of obese women. The presence of maternal hypertension among obese women may be a factor influencing the relationship between placental size and birth weight (90).

Preeclampsia, a problem affecting about 3% of all pregnancies, originates in the placenta (74). Preeclampsia is more common among women with high BMIs. A meta-analysis of maternal BMI and preeclampsia showed that the risk doubled with each 5–7 kg/m^2 increase in BMI (66). There are two broad categories of preeclampsia: (*a*) placental preeclampsia arising from hypoxic state and poor development of the placenta and its maternal blood supply, and (*b*) maternal preeclampsia arising from an interaction between a normal placenta and a maternal low-grade inflammatory response such as obesity, hypertension, or diabetes. In placental preeclampsia, invasion of the trophoblast cells is inhibited by the hypoxic state, the arteries are poorly remodeled, and uteroplacental circulation is inadequate. The hypoxic, dysfunctional placenta releases what is called trophoblast debris into maternal circulation, which causes a generalized systemic inflammatory response. Thus, an

inflammatory response is the outcome of both placental and maternal preeclampsia, but the etiology differs. Placental preeclampsia, or abnormal placentation, has its origins early in gestation; maternal preeclampsia, or maternal subclinical inflammatory response, reflects the metabolic milieu of the mother at conception. Clinically, it is impossible to differentiate the two forms of preeclampsia since the outcome of both is an inflammatory state.

Obese women are more likely than normal-weight women to enter pregnancy in a subclinical inflammatory state since increases in body fat are associated with elevated cytokine levels and subclinical inflammation (39a). Alternatively, maternal adiposity could also produce a hypoxic state if glycosylated hemoglobin levels are increased and affinity for oxygen is reduced, decreasing oxygen transfer to the uterus and impairing normal placentation. Several studies of dietary antioxidants and preeclampsia have been done to prevent or treat the disorder. The results are mixed (86); in some cases, the maternal inflammatory response is improved, but symptoms of preeclampsia are unchanged (74). This may be because antioxidants can improve the inflammatory response associated with preeclampsia, but not the cause.

METABOLISM DURING LATE PREGNANCY

During the last half of pregnancy, the fetus continues to grow and mature its various organ systems, it prepares for the challenge of birth (i.e., breathing on its own), and it also gets ready for postnatal life. As in early pregnancy, these developments are influenced by genetics and the fetal environment (38). The maternal situation determines the fetal environment, i.e., adequacy of the food supply, altitude, infection, etc., which in turn affect the maternal physiological state. Maternal obesity has a marked effect on the maternal physiological state and adjustments to pregnancy. The key gestational adjustments involve circulatory and metabolic changes to provide nourishment and oxygen to the fetus and to remove waste products. These changes are brought about by hormonal changes directly or indirectly induced by the placenta. For example, at mid-pregnancy, the placenta starts making large amounts of estrogens from precursors produced by the fetus. The placenta then produces and secretes several hormones (i.e., placental lactogen and placental growth hormone) into maternal circulation to modify metabolism. In this section, the effect of maternal obesity on the metabolic adjustments in macronutrient metabolism during late pregnancy is reviewed.

Energy Metabolism

The slow rate of fetal growth in humans has a profound effect on energy metabolism during gestation. Since the energy cost of gestation is spread over an extended period, the human energy cost is lower per maternal kilogram metabolic body size than for any other mammal (68). In general, the energy costs are divided into three

components: (*a*) energy deposited in the conceptus as new tissue (~20 MJ or 4780 kcal), (*b*) energy deposited as fat in well-nourished women (~150 MJ or 35,800 kcal), and (*c*) energy required to maintain the new tissue (~150 MJ or 35,800 kcal). The maintenance requirement is estimated as the cumulative increase in maternal basal metabolic rate over the entire period of pregnancy above the prepregnancy value (68). The energy needs for maintaining a pregnancy in humans is about four times greater than the cost for synthesizing the product of conception because the fetus grows slowly and, therefore, requires a longer period of maintenance (68).

The amount of energy used for fat deposition is influenced by the quantity of maternal energy reserves at conception. In a series of international studies in eight nations representing affluent and developing countries, the amount of energy used for fat deposition increased directly with the state of affluence (68) (Figure 1). For example, Swedish women used more than 250 MJ (~60,000 kcal) for fat deposition, whereas women from the Philippines and Thailand only used about 50 MJ (~12,000 kcal) (69). Women from the Gambia who did not receive any nutritional supplements during gestation actually had a decrease in their energy reserves, representing approximately 10 MJ (~2400 kcal). In other words, they mobilized their energy reserves to meet demands for synthesis and maintenance of new tissue.

The effect of maternal adiposity on energy used for fat deposition among individual women in affluent countries is not as clear. In a study of British pregnant women, the net fat gain between 13 and 36 weeks gestation was lower in 25 obese women compared with that of 29 normal-weight women (85). Data from 405 Brazilian women followed for nine months postpartum showed that each unit increase in prepregnancy BMI was associated with a 0.5 kg decrease in postpartum weight retention (48). If we assume that postpartum weight retention reflects fat gain during gestation, this implies that heavier women gained less fat during gestation and, therefore, retained less weight postpartum. On the other hand, a small, but thorough, study of 63 American women showed that 12 overweight women entering pregnancy with a BMI $\geq$26 gained more fat than 34 women with normal BMIs (19.8–26.0) (15). The women with high BMIs also gained more weight during gestation than did normal weight women. Clearly, high gestational weight gains among obese women increase the amount of fat gained.

The rise in the maternal metabolic rate during pregnancy is driven by the metabolic cost of maintaining the conceptus and supporting maternal tissue. Fetal metabolism represents a significant proportion of the total metabolic cost, but the metabolic rates of maternal tissues are elevated during gestation and contribute to the cost. Large population studies of women in upper- and low-income countries show a strong association between maternal prepregnant body fat and the metabolic maintenance costs (69). The marked difference in maintenance costs are illustrated in Figure 1. In well-nourished women, the basal metabolic rate (BMR) begins to rise soon after conception. In undernourished Gambian women, the BMR is suppressed below nonpregnant values into the third trimester so that

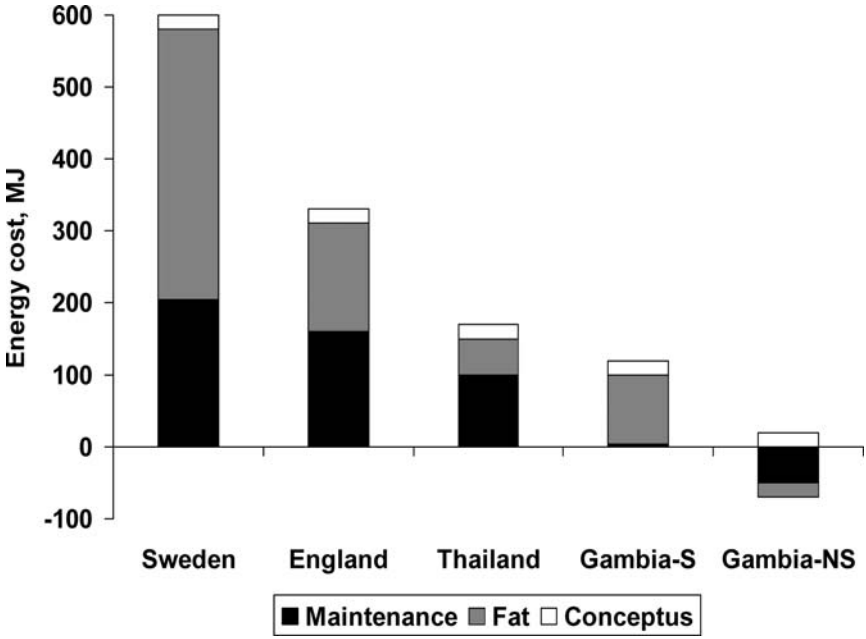

Figure 1 The total energy costs for the conceptus, fat deposition, and maintenance (or basal metabolism) of pregnancy among women from affluent and poor countries. Adapted from Prentice Goldberg (68). Gambia S, supplemented; Gambia NS, non-supplemented.

the cumulative metabolic cost is lower in pregnant than in nonpregnant women (68, 69). This adjustment conserves energy to meet the additional demands for synthesis of new pregnancy tissue in a marginal nutritional state.

Obese women, with ample energy reserves, markedly increase their metabolic rates during gestation compared with nonobese women (12, 17). A cross-sectional study of 16 pregnant women between 31–35 weeks gestation showed that maternal fat mass was a highly significant predictor ($p < 0.001$) of BMR (12). The eight obese women weighed about 30 kg more than the nonobese women did at the time of measurement (102 versus 74 kg), and the total BMR was about 400 kcal/d higher in the obese women (1987 versus 1581 kcal/d). A similar observation was made in a longitudinal study of 63 women from prior to conception to 36 weeks gestation (17). The women entering pregnancy with high BMIs (≥ 26) had significantly higher BMRs throughout gestation. This difference persisted after adjusting for body weight or body fat ($p < 0.003$ or 0.03). In comparison with undernourished women who appear to conserve energy during pregnancy, obese women appear to waste energy by markedly increasing their BMR. Pregnant women normally gain fat reserves during mid-gestation (46). In obese women, additional fat gain is unnecessary and may even be detrimental. An increase in basal energy expenditure

would prevent an unhealthy acquisition of additional adipose tissue. Possibly, the amount of maternal fat stores influences the hormones of pregnancy, which in turn modulate adjustments in maternal energy metabolism.

Thus, total energy costs of pregnancy correlate with maternal fatness as well as pregnancy weight gain. It is impossible to determine which of these factors is dominant because they are highly related (68). Within-country analyses of energy costs during pregnancy in England and The Netherlands found no association between maternal maintenance needs and pregnancy weight gain, which suggests that prepregnancy energy stores are the critical factor. Leptin is a hormone that monitors peripheral energy status and adjusts metabolism accordingly. In pregnancy, leptin may be sensitive to maternal energy status and coordinate the metabolic response accordingly. Serum leptin levels increase significantly in early gestation, possibly due to placental synthesis and secretion (1). Gestational hormones, such as estrogen, may also up-regulate maternal leptin concentrations (16). Among nonpregnant individuals, a negative energy balance causes a decline in circulating leptin levels, which in turn induces food intake and decreases the metabolic rates. In pregnancy, circulating leptin concentrations are correlated with maternal BMI; extremely low levels have been observed in thin African women (16, 30, 70). Low circulating leptin levels may initiate frugal (i.e., energy-sparing) metabolic pathways during gestation. In a small study of 10 women, leptin was significantly correlated with oxygen consumption (i.e., basal energy expenditure) prior to and during gestation (45). However, changes in circulating leptin did not correlate with changes in BMR (20). Larger, more detailed studies are needed to address the relationship between leptin and energy metabolism during pregnancy.

Fuel Metabolism

During late pregnancy, when the fetal growth demands are high, the mother switches her metabolism to provide the fuels needed by the fetus (43). Since glucose is the preferred fuel of the fetus, a modest insulin-resistant state develops, which sustains maternal plasma glucose concentrations for diffusion across the placenta around the clock. In the postabsorptive state, maternal hepatic glycogen stores are mobilized, and hepatic glucose production increases. In the fed state, glucose disposal or tolerance is impaired, and blood glucose levels remain elevated for longer periods following a meal (52) (Figure 2).

Lipid metabolism also undergoes major adjustments during late pregnancy to allow pregnant women to use stored lipid to support their energy needs during the postabsorptive state, to minimize protein catabolism, and to preserve glucose and amino acids for the fetus. The breakdown of fat stores in adipose tissue is enhanced, increasing plasma free fatty acid (FFA) and glycerol levels (43) (Figure 2). In the liver, the FFAs are converted to triglycerides and returned to circulation as very-low-density lipoproteins (VLDLs). Glycerol is a preferred gluconeogenic substrate, conserving amino acids for the fetus. Hyperlipidemia occurs, representing

the increased levels of lipolytic products in circulation combined with enhanced triglyceride production by the liver. Although triglycerides do not cross the placenta, they represent a "floating energy deposit" that is easily accessible by the actions of lipoprotein lipase and other lipases releasing fatty acids that cross the placenta and provide a source of energy for the fetus. During the postabsorptive state, FFAs are also taken up by the liver and undergo beta-oxidation to form ketones (52), making pregnant women very prone to ketosis (61). These ketogenic substrates also cross the placenta and provide fuel for the fetus, or they can be used by maternal tissue for energy and to spare glucose.

Amino acids can follow one or two fates: They can either be retained in tissues or oxidized. The fate of most amino acids during pregnancy is to be used for protein synthesis, and the portion oxidized for energy is reduced. During the first trimester, protein synthesis remains similar to that of nonpregnant women, but in the second and third trimesters, it increases by 15% and 25%, respectively (34). The amount of protein synthesized is greater than that accounted for by the fetus and placenta, which implies an overall increase in protein synthesis in maternal tissues. There is a slight (about 10%) decrease in amino acid oxidation throughout gestation (34). The net increase in protein synthesis is greater than the decline in oxidation, which suggests that amino acids are partitioned toward deposition and away from oxidation. As a result of reduced amino acid oxidation, urea synthesis is decreased, and plasma and urinary urea nitrogen levels decline (49, 50). This decline in urinary urea nitrogen contributes to the positive nitrogen balance measured during late pregnancy (51).

Because only a limited number of studies have been done, very little information is available on the effect of maternal obesity on the shifts in fuel metabolism during pregnancy. However, the high prevalence of metabolic complications among obese pregnant women suggests that obesity exacerbates the usual metabolic adjustments in fuel metabolism. Normal human pregnancy is associated with hyperinsulinemia and a progressive decline in insulin sensitivity from early to late pregnancy (25, 36). This metabolic adjustment appears to be magnified in obese women. Both peripheral and hepatic insulin resistance was increased in glucose-tolerant obese women when they were compared with normal or lean subjects; peripheral insulin sensitivity was about 40% lower in the obese women (84). Furthermore, the insulin response to an intravenous glucose infusion was reduced in obese compared with lean pregnant women, a finding that suggests a chronic depression in insulin sensitivity in obese women leading to compensatory basal hyperinsulinemia (22). In the postprandial state, this insulin resistance associated with obesity exaggerated the usual circulatory increases in metabolic fuels (i.e., glucose, lipids, and amino acids), allowing excess nutrients to be shunted to the fetus (14). In fact, the fasting, postprandial, and integrated 24-hour plasma concentrations of all three macronutrients are affected by enhanced insulin resistance in obese women. The impaired glucose uptake exposes the fetus to hyperglycemia; the inability to suppress whole body lipolysis leads to an increase in plasma FFA, and the decreased ability of

insulin to suppress amino acid turnover causes an elevation in circulating levels of branched-chain amino acids (23, 60).

Women with upper-body obesity may have a metabolic response to pregnancy that differs from that of women with lower-body obesity (55). Those with upper body obesity have an earlier maximal insulin and glucose response to an oral glucose load in comparison with lean women or women with lower-body obesity. The state of being pregnant may also further enhance upper-body fat stores in obese women: Ehrenberg and coworkers found that obese women deposit more fat reserves centrally in the upper-body area, i.e., the suprailiac and subscapular regions, than do lean women (35).

Hyperlipidemia is also exaggerated in obese pregnant women (71). The inability of insulin to suppress whole-body lipolysis leads to a marked increase in plasma FFA in obese and gestational diabetes mellitus (GDM) patients relative to controls (95). Given that obese women start with higher levels of FFA concentrations, further resistance to lipolysis during gestation magnifies the amount of plasma FFA. Obese women also experience higher serum triglyceride levels packaged into VLDLs as well as low- and high-density lipoproteins (44, 71). Triglycerides in plasma lipoproteins do not cross the placenta. But they are hydrolyzed by the placenta, where they are reesterified to provide a FFA reserve (44). In this way, essential fatty acids derived from the maternal diet are transported to the fetus.

The marked increases in serum lipids in obese pregnant women are attributed to the enhanced insulin-resistant condition and to an increase in plasma estrogen (44) since adipose tissue is the primary source of estrogen. Catalano and coworkers (19) found that insulin receptor substrate-1 protein levels in the adipose tissue of obese women with GDM were 43% lower than that of controls. This would account, at least in part, for the increase in insulin resistance seen in obese women. Circulating levels of peroxisome proliferator-activated receptor-γ (PPARγ) mRNA and protein are also reduced in obese women with GDM compared with healthy women (19). Since PPARγ plays an important role in regulating lipid storage by adipose tissue and is implicated in the regulation of systemic insulin sensitivity, its reduction may play a key role in the insulin suppression of lipolysis.

The effect of obesity on amino acid oxidation and protein synthesis has not been studied during pregnancy. A study in nonpregnant obese women showed that protein synthesis was simulated less in a hyperinsulinemic state in comparison with lean women; there were no differences in protein oxidation (26). Duggleby & Jackson (33) measured protein turnover in 25 pregnant women during the second trimester. A multivariate analysis of the data showed that mothers with higher amounts of visceral lean tissue had higher rates of protein turnover compared with women with less visceral lean tissue. Also, higher rates of protein turnover at 18 weeks gestation were associated with longer babies at birth. Maternal fatness was not related to protein turnover, however. Further studies need to be done to evaluate the effect of a hyperinsulinemic state on protein turnover in obese pregnant women.

FETAL GROWTH AND DEVELOPMENT IN LATE PREGNANCY

The enhanced insulin resistance observed in obese pregnant women increases fetal exposure to all major fuel sources—glucose, FFAs, ketones, and amino acids. Thus, it is not surprising that obese mothers deliver LGA infants 1.4 to 1.8 times more frequently than do lean mothers (37). It is striking that prepregnancy obesity is independently and strongly associated with LGA, whereas net weight gain during pregnancy has only a modest effect (72). As described above, maternal obesity is associated with hyperglycemia and hyperlipidemia during gestation. A large body of evidence indicates that substrate delivery to the placenta is the primary maternal factor regulating fetal growth (28). A rise in the flow and/or availability of maternal substrate levels is thought to decrease the placental release of growth-suppressive peptides, which enhances fetal growth rates by increasing the expression of insulin-like growth factors and decreasing their binding proteins (28). Thus, the association between maternal adiposity and fetal size probably reflects the metabolic shifts in fuel metabolism in obese compared with nonobese women. This is verified by that fact that late in the third trimester, when insulin resistance reaches its peak and circulating glucose levels are the highest, maternal glycemia is more strongly associated with LGA than is maternal BMI (78). Also, addition of hyperlipidemia to the presence of hyperglycemia improves the ability to predict the risk of LGA babies (9), which implies that fetal macrosomia likely results from an increased supply of lipids as well as glucose.

Exposure to maternal diabetes not only affects fetal size, but also alters fetal body composition (24, 54). Asymmetric macrosomia (high fetal fat relative to fetal length) is commonly reported in type 1, type 2, and gestational diabetes and even with modest elevations of maternal glucose levels (24, 62). This increase in fetal fatness appears to be specific for women with some degree of glucose intolerance, as LGA infants born to women with normal glucose tolerance do not seem to have increased amounts of fetal fat (24). The increase in fetal fat among infants exposed to maternal diabetes is thought to reflect an increase in fetal glucose supply, which in turn induces fetal insulin secretion and storage of excess glucose as fat.

A recent study shows that maternal diabetes also alters fetal growth patterns by reducing chondrogenesis and increasing adipogenesis in specific organs or tissues (54). In a study of 37 fetuses of diabetic mothers, exposure to diabetes altered growth patterns of the head, limbs, and abdomen in the second and third trimesters compared with that of 29 unexposed fetuses. Although a greater abdominal circumference is well known among macrosomic infants (8), the effect of diabetes on head and limb proportions has not been observed previously (54). The occipito-frontal diameter was decreased, the upper limbs were relatively long compared with lower limbs, and the limb length to limb circumference (volume) was reduced in the exposed fetuses. It appeared that adipogenesis was given preference over chondrogenesis in certain tissues among women with elevated levels of hemoglobin A1c. The authors hypothesize that these unique shifts in the fetal

growth pattern reflect a hyperglycemic/hypoxemic situation. They speculate that hypoxia results from glycosylated hemoglobin's increased oxygen affinity making it less available for maternal-fetal transfer and fetal cellular respiration and that this hypoxemia in the presence of excess energy from glucose leads to alterations in fetal growth.

These effects of fetal exposure to hyperglycemia on body size, composition, and organ/tissue structure help explain why in utero development influences long-term physiological function and health. Data showing a link between the fetal experience and subsequent risk for disease have been reviewed extensively elsewhere (4–7, 39, 41); only the impact of maternal obesity or diabetes is mentioned here. Studies have found that children born to diabetic mothers are at greater risk for becoming obese (31, 83), developing type 2 diabetes (31, 83), and having the metabolic syndrome (11). Also, children exposed to maternal obesity without GDM are at increased risk of becoming obese (93) and developing the metabolic syndrome (11). Although most of the studies to date have focused on the effects of exposure to maternal diabetes and fetal growth, it appears that maternal obesity per se without diabetes also alters the metabolic environment and places the child's postnatal health at risk.

MATERNAL DIET AND PREGNANCY OUTCOMES

There is ample evidence showing that maternal obesity increases the risk of metabolic complications (i.e., gestational diabetes, pregnancy-induced hypertension, and preeclampsia) and alters fetal growth and risk for disease postnatally. But little attention has been paid to how to prevent these problems. Maternal diet, as a key component of the maternal environment, likely contributes to the risk as well as the prevention of these metabolic complications. Although the studies of maternal diet and pregnancy complications have been done primarily in nonobese women, the findings persist after adjusting for body weight or BMI, suggesting that the results are applicable to obese as well as to nonobese women.

In the past, much of the nutritional therapy for GDM patients focused on energy restriction because lower calorie intakes controlled glycemia and reduced macrosomia (53, 67). However, given concern about the effect of maternal ketosis induced by energy restriction on fetal neurophysiological and cognitive development, the focus shifted from reducing energy intakes to adjusting carbohydrate and fat intakes for women with gestational glucose intolerance. Currently, the American Diabetes Association limits energy intake for overweight compared to normal-weight women. For example, 36–40 kcal/kg are recommended for women with body weights <90% of standard, whereas 24 kcal/kg are recommended for women weighing between 121% and 150% of standard. Only 12–18 kcal/kg are recommended when ideal body weight exceeds 150% of standard. These energy recommendations are less than that recommended by the Institute of Medicine for pregnancy (59), but are higher than the energy levels fed in early studies of GDM (53, 58). The American Diabetes Association also recommends that carbohydrate

and fat intake each be 40% of total energy, with the remaining 20% from protein (32). This was updated in 2004 to suggest a range in carbohydrate intake from 45% to 65% of the total calories to be consistent with the new Dietary Reference Intakes (82). No specific recommendation was made regarding the type of carbohydrate, however.

Dietary Carbohydrate

Given that maximal maternal-fetal glucose transfer occurs postprandially (32), reducing glucose concentrations at this time has a greater impact on limiting accelerated fetal growth than on lowering fasting glucose levels. Thus, studies have begun to investigate how to reduce postprandial glycemia and thereby lessen fetal glucose exposure. Low-glycemic-load diets have been shown in several small studies of pregnant women to reduce the glycemic response to meals and to improve insulin sensitivity in mid and late pregnancy, thereby reducing placental and birth weights and neonatal fat mass (27, 28). Since a low dietary glycemic load reduces fetal glucose levels, this diet is also associated with approximately a twofold increased risk of an SGA birth (79). Obviously, if total carbohydrate intake is limited along with a shift toward low-glycemic foods, the postprandial glycemic spikes will be reduced and fetal glucose supply may be inadequate to support fetal growth. Research is needed to determine optimal levels of glycemic load for obese pregnant women to prevent excessive fetal growth without inducing SGA.

Although GDM women are advised to limit the amount of carbohydrate intake to 40% of total energy to maintain good glycemic control (32, 47, 58), a shift toward more complex carbohydrates should permit higher total carbohydrate intakes with a comparable glycemic response. When low-glycemic sources are the basis of the diet, up to 60% of the energy can be given as carbohydrate to pregnant diabetic women without any detrimental effect on glucose tolerance (32). It has also been shown that diabetic, pregnant women fed diets providing 65% of the energy as carbohydrate and 60–70 g fiber required less exogenous insulin than did women consuming 40% carbohydrate diets with 20 g fiber (65). Epidemiological studies have also shown that 100-kcal increases in carbohydrate to the diet were associated with a 12% decrease in risk of impaired glucose tolerance and a 9% decrease in the risk of GDM (77). In other words, substituting carbohydrate for fat significantly decreased the risk of poor glycemic control. Thus, limiting dietary carbohydrate among pregnant women to avoid excessive postprandial glucose spikes seems to be unnecessary if low-glycemic, complex carbohydrates form the basis of the diet.

Dietary Fat

Lowering the level of carbohydrate in a diet implies increased levels of fats. Evidence is now accumulating that a high fat intake is linked to insulin resistance and a higher risk of gestational diabetes. The type and the amount of dietary fat both seem to play a role. For example, the recurrence of GDM is significantly higher among women consuming diets providing about 40% of the energy as fat compared with that of women consuming lower-fat (about 33%) diets (63). This

relationship could reflect a lower intake of fiber and complex carbohydrates since these dietary factors are usually inversely related to fat intake. Conversely, high intakes of polyunsaturated fats are associated with better pregnancy outcomes, and they may even be protective of impaired glucose tolerance (IGT) or GDM (10, 91). These relationships persist after controlling for body weight or BMI. A high saturated fat intake also is related to the risk for IGT or GDM (10). All women consuming more than 30% of their total energy as saturated fat (about three times recommended intakes) had IGT or GDM; no similar cutoff was evident for high polyunsaturated fatty acid intakes. Furthermore, a high intake of saturated fat was the only factor linked to the development of IGT or GDM in young, normal-weight women lacking other risk factors for this disease, which suggests that modifying fat intakes prior to and during pregnancy could be an effective way to prevent gestational glucose intolerance.

Diet Recommendations

As mentioned above, the current recommendations by the American Diabetes Association specify amounts of carbohydrate and fat intake for preventing or treating gestational glucose intolerance. Maintaining carbohydrate and fat intakes within the acceptable macronutrient distribution ranges recommended by the Institute of Medicine (46a) would allow more flexibility in dietary planning without appreciably altering risk of IGT. At the same time, it seems prudent to also consider types of carbohydrate and fat when managing the diets of pregnant women at risk for IGT. Emerging evidence suggests an emphasis on high-complex, high-fiber, low-glycemic sources of carbohydrate while increasing the intake of polyunsaturated fat acids and limiting saturated fat intake. The 2005 Dietary Guidelines for Americans provide guidance consistent with this dietary pattern for nonpregnant women. The following adaptations from the 2005 Dietary Guidelines may serve as the basis of a sound dietary pattern for pregnant women (80).

- Keep total fat intake between 20% and 35% of the calories and total carbohydrate intake between 45% and 65% of the calories.
- Choose fiber-rich fruits, vegetables, and whole grains often. In general, consume at least 2 cups of fruit, $2^1/_2$ cups of vegetables, and 3 ounces of whole-grain products daily.
- Choose most fats from good sources of polyunsaturated fatty acids, such as fish, nuts, and vegetable oils, and limit the intake of saturated fatty acids to less than 10% of the calories each day.

PERSPECTIVES

There is substantial evidence that maternal obesity alters the course of pregnancy. In early pregnancy, placental and embryonic development is affected. In late pregnancy, maternal metabolic complications and alterations in fetal size and body

fat occur. The in utero environment of obese women appears to force the fetus to metabolic adjustments that influence immediate and long-term development. These adjustments may not be consistent with good health in the postnatal environment. Ways to prevent or reduce metabolic aberrations in obese pregnant women have not been identified. Maternal diet seems to play a substantial role, but the effects of preconceptional and gestational diet need further study. In preparation for pregnancy, obese women are often advised to lose weight. However, exposure to undernutrition during the periconceptional period may also be inconsistent with good pregnancy outcomes. It is prudent, therefore, to proceed with caution when advising obese women about diet prior to and during gestation.

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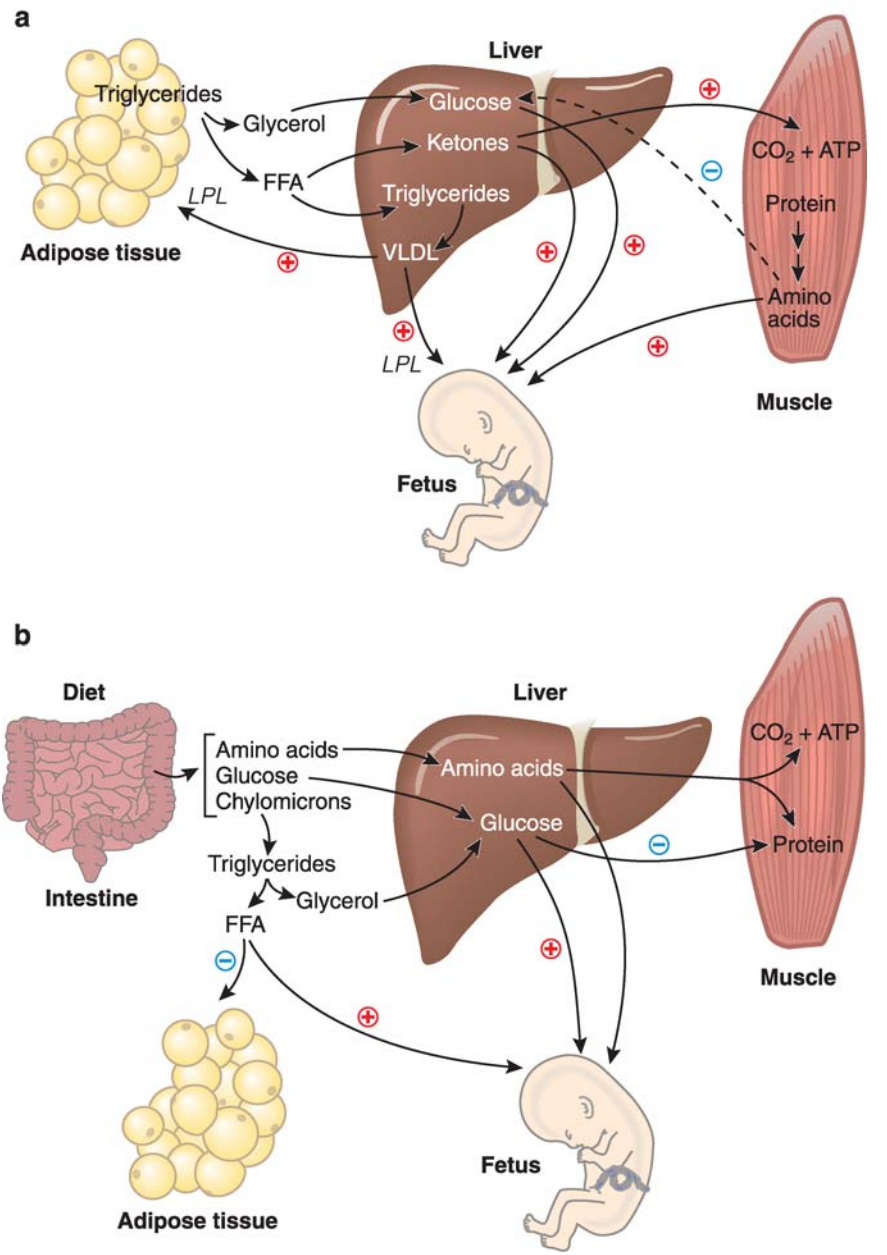

Figure 2 Schematic representation of the effect of pregnancy on carbohydrate, lipid, and amino acids metabolism. Arrows with (+) markings are those pathways enhanced during late pregnancy; arrows with (−) markings are those reduced. In general, these metabolic shifts are more enhanced in obese than in normal-weight women. *Part a* shows the response in a postabsorptive state; *part b* depicts a postprandial state. FFA, free fatty acids; VLDL, very-low-density lipoproteins; LPL, lipoprotein lipase. Adapted from Herrera (43, 44).

Annual Review of Nutrition
Volume 25, 2005

CONTENTS

DIETARY FIBER: HOW DID WE GET WHERE WE ARE?, *Martin Eastwood and David Kritchevsky* 1

DEFECTIVE GLUCOSE HOMEOSTASIS DURING INFECTION, *Owen P. McGuinness* 9

HUMAN MILK GLYCANS PROTECT INFANTS AGAINST ENTERIC PATHOGENS, *David S. Newburg, Guillermo M. Ruiz-Palacios, and Ardythe L. Morrow* 37

NUTRITIONAL CONTROL OF GENE EXPRESSION: HOW MAMMALIAN CELLS RESPOND TO AMINO ACID LIMITATION, *M.S. Kilberg, Y.-X. Pan, H. Chen, and V. Leung-Pineda* 59

MECHANISMS OF DIGESTION AND ABSORPTION OF DIETARY VITAMIN A, *Earl H. Harrison* 87

REGULATION OF VITAMIN C TRANSPORT, *John X. Wilson* 105

THE VITAMIN K-DEPENDENT CARBOXYLASE, *Kathleen L. Berkner* 127

VITAMIN E, OXIDATIVE STRESS, AND INFLAMMATION, *U. Singh, S. Devaraj, and Ishwarlal Jialal* 151

UPTAKE, LOCALIZATION, AND NONCARBOXYLASE ROLES OF BIOTIN, *Janos Zempleni* 175

REGULATION OF PHOSPHORUS HOMEOSTASIS BY THE TYPE IIa Na/PHOSPHATE COTRANSPORTER, *Harriet S. Tenenhouse* 197

SELENOPROTEIN P: AN EXTRACELLULAR PROTEIN WITH UNIQUE PHYSICAL CHARACTERISTICS AND A ROLE IN SELENIUM HOMEOSTASIS, *Raymond F. Burk and Kristina E. Hill* 215

ENERGY INTAKE, MEAL FREQUENCY, AND HEALTH: A NEUROBIOLOGICAL PERSPECTIVE, *Mark P. Mattson* 237

REDOX REGULATION BY INTRINSIC SPECIES AND EXTRINSIC NUTRIENTS IN NORMAL AND CANCER CELLS, *Archana Jaiswal McEligot, Sun Yang, and Frank L. Meyskens, Jr.* 261

REGULATION OF GENE TRANSCRIPTION BY BOTANICALS: NOVEL REGULATORY MECHANISMS, *Neil F. Shay and William J. Banz* 297

POLYUNSATURATED FATTY ACID REGULATION OF GENES OF LIPID METABOLISM, *Harini Sampath and James M. Ntambi* 317

SINGLE NUCLEOTIDE POLYMORPHISMS THAT INFLUENCE LIPID METABOLISM: INTERACTION WITH DIETARY FACTORS, *Dolores Corella and Jose M. Ordovas* 341

THE INSULIN RESISTANCE SYNDROME: DEFINITION AND DIETARY APPROACHES TO TREATMENT, *Gerald M. Reaven* 391

DEVELOPMENTAL DETERMINANTS OF BLOOD PRESSURE IN ADULTS, *Linda Adair and Darren Dahly* 407

PEDIATRIC OBESITY AND INSULIN RESISTANCE: CHRONIC DISEASE RISK AND IMPLICATIONS FOR TREATMENT AND PREVENTION BEYOND BODY WEIGHT MODIFICATION, *M.L. Cruz, G.Q. Shaibi, M.J. Weigensberg, D. Spruijt-Metz, G.D.C. Ball, and M.I. Goran* 435

ANNUAL LIPID CYCLES IN HIBERNATORS: INTEGRATION OF PHYSIOLOGY AND BEHAVIOR, *John Dark* 469

DROSOPHILA NUTRIGENOMICS CAN PROVIDE CLUES TO HUMAN GENE–NUTRIENT INTERACTIONS, *Douglas M. Ruden, Maria De Luca, Mark D. Garfinkel, Kerry L. Bynum, and Xiangyi Lu* 499

THE COW AS A MODEL TO STUDY FOOD INTAKE REGULATION, *Michael S. Allen, Barry J. Bradford, and Kevin J. Harvatine* 523

THE ROLE OF ESSENTIAL FATTY ACIDS IN DEVELOPMENT, *William C. Heird and Alexandre Lapillonne* 549

INDEXES

Subject Index 573

Cumulative Index of Contributing Authors, Volumes 21–25 605

Cumulative Index of Chapter Titles, Volumes 21–25 608

ERRATA

An online log of corrections to *Annual Review of Nutrition* chapters may be found at http://nutr.annualreviews.org/