Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus[1–5]

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ABSTRACT This article reviews maternal metabolic strategies for accommodating fetal nutrient requirements in normal pregnancy and in gestational diabetes mellitus (GDM). Pregnancy is characterized by a progressive increase in nutrient-stimulated insulin responses despite an only minor deterioration in glucose tolerance, consistent with progressive insulin resistance. The hyperinsulinemic-euglycemic glucose clamp technique and intravenous-glucose-tolerance test have indicated that insulin action in late normal pregnancy is 50–70% lower than in nonpregnant women. Metabolic adaptations do not fully compensate in GDM and glucose intolerance ensues. GDM may reflect a predisposition to type 2 diabetes or may be an extreme manifestation of metabolic alterations that normally occur in pregnancy. In normal pregnant women, basal endogenous hepatic glucose production (R_a) was shown to increase by 16–30% to meet the increasing needs of the placenta and fetus. Total gluconeogenesis is increased in late gestation, although the fractional contribution of total gluconeogenesis to R_a, quantified from ^2H enrichment on carbon 5 of glucose (65–85%), does not differ in pregnant women after a 16-h fast. Endogenous hepatic glucose production was shown to remain sensitive to increased insulin concentration in normal pregnancy (96% suppression), but is less sensitive in GDM (80%). Commensurate with the increased rate of glucose appearance, an increased contribution of carbohydrate to oxidative metabolism has been observed in late pregnancy compared with pregravid states. The 24-h respiratory quotient is significantly higher in late pregnancy than postpartum. Recent advances in carbohydrate metabolism during pregnancy suggest that preventive measures should be aimed at improving insulin sensitivity in women predisposed to GDM. Further research is needed to elucidate the mechanisms and consequences of alterations in lipid metabolism during pregnancy. *Am J Clin Nutr* 2000;71(suppl):1256S–61S.

KEY WORDS Carbohydrate, lipid, metabolism, pregnancy, gestational diabetes mellitus, insulin sensitivity, women

INTRODUCTION

Changes in carbohydrate and lipid metabolism occur during pregnancy to ensure a continuous supply of nutrients to the growing fetus despite intermittent maternal food intake. These metabolic changes are progressive and may be accentuated in women who develop gestational diabetes mellitus (GDM). Application of stable-isotope tracers in conjunction with respiration calorimetry, the hyperinsulinemic-euglycemic glucose clamp technique, and the computer-assisted intravenous-glucose-tolerance test has furthered our understanding of metabolic adaptations during pregnancy. The objective of this article is to review recent advances in our understanding of carbohydrate and lipid metabolism during normal pregnancy and in GDM.

CARBOHYDRATE METABOLISM DURING NORMAL PREGNANCY

Increased insulin secretion and decreased insulin sensitivity

During early pregnancy, glucose tolerance is normal or slightly improved and peripheral (muscle) sensitivity to insulin and hepatic basal glucose production is normal (1–3). The hyperinsulinemic-euglycemic glucose clamp technique and computer-assisted intravenous-glucose-tolerance test indicate greater-than-normal sensitivity to the blood glucose–lowering effect of exogenously administered insulin in the first trimester than in the second and third trimesters. Insulin responses to oral glucose are also greater in the first trimester than before pregnancy. These observations are consistent with a 120% increase at 12–14 wk gestation in the first phase of insulin response, which refers to the change in insulin concentration relative to the elevation in glucose concentration from 0 to 5 min after intravenous glucose administration. The second phase of insulin response, which refers to the rate of insulin release relative to the glucose concentration 5 to 60 min after intravenous glucose administration, is not significantly different in early pregnancy from the pregravid state. The cause of the enhanced insulin secretion is uncertain

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because peripheral insulin sensitivity and hepatic glucose production rates are not different from pregravid values. This metabolic milieu under the influence of cortisol, estrogens, and progestins favors lipogenesis and fat storage.

Longitudinal studies of glucose tolerance during gestation show a progressive increase in nutrient-stimulated insulin responses despite an only minor deterioration in glucose tolerance, consistent with progressive insulin resistance (4). The hyperinsulinemic-euglycemic glucose clamp technique and computer-assisted intravenous-glucose-tolerance test indicate that insulin action in late normal pregnancy is 50–70% lower than that of normal, nonpregnant women (1–3, 5, 6). A progressive increase in basal and postprandial insulin concentrations is seen with advancing pregnancy. By the third trimester, basal and 24-h mean insulin concentrations may double (7). The first and second phases of insulin release are 3- to 3.5-fold greater in late pregnancy (1). Obese pregnant women also develop peripheral and hepatic insulin resistance during the third trimester of pregnancy (8). The hyperinsulinemic-euglycemic glucose clamp technique indicates that insulin-stimulated glucose disappearance, carbohydrate oxidation, and suppression of endogenous glucose production in obese women are reduced in the third compared with the second trimester.

Although the precise mechanism is uncertain, alterations in the hormonal milieu during pregnancy are probably responsible for the reduced insulin sensitivity. Changes in β cell responsiveness occur in parallel with growth of the fetoplacental unit and its elaboration of hormones such as human chorionic somatomammotropin (HCS), progesterone, cortisol, and prolactin. Prevailing insulin resistance produces exaggerated changes in postprandial concentrations of metabolic fuels (eg, glucose, VLDL, and amino acids). Insulin resistance serves to shunt ingested nutrients to the fetus after feeding.

Increased hepatic glucose production

In early pregnancy, basal glucose and insulin concentrations do not differ significantly from nongravid values (2). Basal hepatic glucose production, estimated by using [6,6-$^2H_2$]glucose, do not differ at 12–14 wk of gestation. By the third trimester, however, basal glucose concentrations are 10–15 mg/dL (0.56–0.83 mmol/L) lower and insulin is almost twice the concentration of nongravid women. Postprandial glucose concentrations are significantly elevated and the glucose peak is prolonged (9). Basal endogenous hepatic glucose production (R_a) increases by 16–30% to meet the increasing needs of the placenta and fetus (2, 10, 11). Glucose production increases with maternal body weight, such that glucose production per kilogram body weight does not change throughout pregnancy (11). Endogenous glucose production remains sensitive to increased insulin concentration throughout gestation (90% suppression), in contrast with the progressive decrease in peripheral insulin sensitivity.

Gluconeogenesis was estimated from the appearance of ^2H on carbons 5 and 6 of glucose after ^2H labeling of the body water pool of normal pregnant women at 10 and 34 wk of gestation (12). Total gluconeogenesis is increased in late gestation, although the fractional contribution of gluconeogenesis via pyruvate measured by ^2H enrichment on carbon 6 of glucose (45–61%) and the contribution of total gluconeogenesis to glucose production, quantified from ^2H enrichment on carbon 5 of glucose (65–85%), are not different in pregnant women than in nonpregnant women after a 16-h fast (12). As plasma β-hydroxybutyrate increases, the fractional contribution of gluconeogenesis increases.

Increased carbohydrate use

Commensurate with the increased rate of glucose appearance, studies have shown an increased contribution of carbohydrate to oxidative metabolism in late pregnancy. Measured by respiration calorimetry, the 24-h respiratory quotient (RQ) is significantly higher in late pregnancy than postpartum, such that carbohydrate oxidation as a percentage of nonprotein energy expenditure decreases from 66% to 58% from late pregnancy to 6 mo postpartum (13). Absolute rates of carbohydrate oxidation are significantly higher in pregnancy (282 g/d) than postpartum (210 g/d). RQs during measurements of basal metabolic rate and sleeping metabolic rate are also higher during pregnancy.

In late gestation, rising concentrations of HCS, prolactin, cortisol, and glucagon exert antiinsulinogenic and lipolytic effects that promote greater use of alternative fuels, especially fatty acids, by peripheral tissues. Despite elevated fasting serum prolactin, cortisol, glucagon, and fatty acid concentrations and lowered glucose concentrations, we did not observe a lower RQ or greater use of fatty acids in late pregnancy. On the contrary, as pointed out above, we observed higher mean RQs for 24-h total energy expenditure, sleeping metabolic rate, and basal metabolic rate in late pregnancy than in the postpartum period (13). RQ gradually decreases during the night fast and the proportion of carbohydrate oxidized becomes progressively smaller in the postprandial period, but the fall in RQ was less precipitous then than postpartum. Higher basal RQs were observed in pregnancy by several investigators (14–16). These observations agree with the increased glucose production reported in fasted pregnant women, despite lower fasting plasma glucose concentration. The higher RQ may reflect the obligatory glucose use of the fetus, which uses an estimated 20–25 g glucose/d in late gestation, well within the increment in carbohydrate oxidation seen in our study.

Gestational diabetes mellitus

GDM is defined as "carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy" (17). GDM is a heterogeneous disorder in which age, obesity, and genetic background contribute to the severity of the disease. Women with GDM are at risk for later development of type 2 diabetes. Only a 1.6% incidence of islet cell antibodies are found by using a specific monoclonal antibody in women with GDM (18). GDM is accompanied by alterations in fasting, postprandial, and integrated 24-h plasma concentrations of amino acids, glucose, and lipids. These changes include a 3-fold increase in plasma triacylglycerol concentrations during the third trimester of pregnancy, elevation of plasma fatty acids, delayed postprandial clearance of fatty acids, and elevation of the branched-chain amino acids (19).

The pathophysiology of GDM remains controversial; GDM may reflect a predisposition to type 2 diabetes expressed under the metabolic conditions of pregnancy or it may represent the extreme manifestation of metabolic alterations that normally occur in pregnancy. GDM is not due to defective secretion of insulin or to disproportionate secretion of proinsulin or glucagon (4). Only quantitative differences in insulin secretion have been observed between women with GDM and normal pregnant women. Evidence supports the view that GDM is related to a pronounced peripheral resistance to insulin.

Carbohydrate metabolism has been studied by using an intravenous-glucose-tolerance test and hyperinsulinemic-euglycemic clamp with [6,6-^2H]glucose before conception and in early and

late gestation in nonobese women who were predisposed to and developed GDM (3). Basal endogenous glucose production increases similarly in patients with GDM and in control subjects throughout gestation. An increase in first-phase insulin response is observed in control subjects and in patients with GDM with advancing pregnancy; however, the increase is greater in control subjects. In late pregnancy, insulin suppression of hepatic glucose production is less in patients with GDM (80%) than in control subjects (96%). Catalano et al (3) found that decreased insulin-stimulated glucose disposal preceded the development of decreased insulin response in women with GDM and was evident before pregnancy. The relative decrease in first-phase insulin response, as the first manifestation of β cell dysfunction, and impaired suppression of hepatic glucose production becomes evident only after progressive decreased insulin sensitivity in late gestation, resulting in hyperglycemia.

In overweight patients with GDM, similar rates of fasting glucose appearance are achieved, but with elevated insulin concentrations relative to nondiabetic pregnant control subjects (20). Oxygen consumption, carbon dioxide production, and RQ are similar in patients with GDM and control subjects.

We studied substrate utilization in women with insulin-treated GDM and in healthy control subjects at 32–36 wk of gestation and 6 wk postpartum by using respiration calorimetry and ^{13}C-labeled substrates (21). Total energy expenditure, basal metabolic rate, and whole-body net carbohydrate and fat utilization did not differ significantly between insulin-treated patients with GDM and control subjects. Exogenous (dietary) glucose oxidation was determined by ^{13}C recovered in breath carbon dioxide from [^{13}C]glucose. The time to peak $^{13}CO_2$ enrichment did not differ significantly between groups, indicating similar rates of delivery of substrate to the site of oxidation. ^{13}C recovery from [^{13}C]glucose was not significantly different between patients with GDM and control subjects, or between antepartum and postpartum time intervals. These findings are consistent with previous studies of well-controlled GDM during pregnancy (10, 22, 23).

Controversy exists regarding the effectiveness of tight glucose control for reducing macrosomia in GDM (24). Recent findings from the Diabetes in Early Pregnancy Trial indicate that postprandial glucose concentrations, not fasting concentrations, are predictive of birth weight (25). A lack of association between birth weight and plasma glucose concentrations in other studies may be due to differences in study design, treatment, the extent to which glucose control was documented accurately, and method of analysis. Positive correlations between maternal basal plasma free fatty acids and triacylglycerols and birth weight have been reported in diabetic pregnancies, suggesting that lipid flux across the fetoplacental unit may contribute to macrosomia.

LIPID METABOLISM DURING NORMAL PREGNANCY AND IN GDM

Changes in hepatic and adipose metabolism alter circulating concentrations of triacylglycerols, fatty acids, cholesterol, and phospholipids (7). After an initial decrease in the first 8 wk of pregnancy, there is a steady increase in triacylglycerols, fatty acids, cholesterol, lipoproteins, and phospholipids. The higher concentration of estrogen and insulin resistance are thought to be responsible for the hypertriglyceridemia of pregnancy.

Cholesterol is used by the placenta for steroid synthesis and fatty acids are used for placental oxidation and membrane formation. Changes in total cholesterol concentration reflect changes in the various lipoprotein fractions. HDL cholesterol increases by 12 wk of gestation in response to estrogen and remains elevated throughout pregnancy (26). Total and LDL-cholesterol concentrations decrease initially, but then increase in the second and third trimesters. VLDL and triacylglycerols decrease in the first 8 wk of gestation and then continuously increase until term. In the second half of pregnancy, VLDL clearance is altered because of the decreased activity of lipoprotein lipase (LPL) in the adipose and liver and because of the increased activity in the placenta. In the fed state, hepatic LPL is low, but increases with fasting, which increases fatty acid and ketone production for the fetus while the supply of glucose is low.

Changes in lipid metabolism promote the accumulation of maternal fat stores in early and mid pregnancy and enhance fat mobilization in late pregnancy. In early pregnancy, increased estrogen, progesterone, and insulin favor lipid deposition and inhibit lipolysis. LPL activity in the adipose tissue from the femoral region, but not from the abdominal region, is elevated at 8–11 wk of gestation (27). Lipolysis in response to catecholamines is markedly higher in the abdominal than in the femoral region. The femoral cells are virtually unresponsive to catecholamines in pregnancy.

In late pregnancy, HCS promotes lipolysis and fat mobilization. The increase in plasma fatty acid and glycerol concentrations is consistent with mobilization of lipid stores. This shift from an anabolic to a catabolic state promotes the use of lipids as a maternal energy source while preserving glucose and amino acids for the fetus. With prolonged fasting (48 h), as well as shorter periods of fasting (18 h), there is a rapid diversion of maternal metabolism to fat oxidation, with an elaboration of ketones (19). Decreases in plasma glucose, insulin, and alanine, and increases in plasma fatty acid and β-hydroxybutyrate are seen in pregnant women hours before these changes are seen in nonpregnant women (28). The enhanced lipolysis and ketogenesis allow pregnant women to utilize stored lipid to subsidize energy needs and minimize protein catabolism.

GDM induces a state of dyslipidemia consistent with insulin resistance. During pregnancy, women with GDM do have higher serum triacylglycerol concentrations but lower LDL-cholesterol concentrations than do normal pregnant women (29). Total cholesterol, HDL cholesterol, and apolipoprotein concentrations are not significantly different between GDM patients and control subjects.

Recovery of exogenously administered [^{13}C]Hiolein (Martek, Columbia, MD), a biosynthetic triacylglycerol, as breath $^{13}CO_2$ is significantly higher antepartum than postpartum (21). The cumulative dose recovery as breath $^{13}CO_2$ is significantly lower in the patients with GDM antepartum and postpartum, indicating lower oxidation of exogenous triacylglycerols. The mechanism underlying the lower recovery of [^{13}C]Hiolein as $^{13}CO_2$ is unclear, but possibilities include the following: *1*) decreased hydrolysis, *2*) reduced fatty acid uptake and subsequent oxidation, and *3*) increased hepatic oxidation and esterification of fatty acid in support of increased synthesis of VLDL. Higher plasma insulin may suppress fatty acid oxidation. With a hyperinsulinemic-euglycemic clamp and [^{2}H]glycerol and [^{13}C]palmitate, insulin was shown to decrease fatty acid oxidation by 55% and lipolysis by 71% and to completely suppress extracellular fatty acid reesterification in healthy subjects (30). The reduced oxidation of exogenously

administered [^{13}C]Hiolein must have been counterbalanced by a greater contribution of intracellular lipid stores to whole-body lipid oxidation, because this did not differ between patients with GDM and control subjects as measured by 24-h calorimetry. We speculate that lower oxidation of exogenous (dietary) triacylglycerols in GDM may allow greater availability of triacylglycerols to the fetoplacental unit. Fatty acids derived from maternal triacylglycerols cross the placenta and could contribute to fetal macrosomia.

REPRODUCTION AND METABOLIC FUEL AVAILABILITY

Reproductive viability is closely linked to metabolic fuel availability (31). Neural mechanisms controlling the pulsatile release of gonadotropin-releasing hormone, luteinizing hormone secretion, and ovarian function respond to minute-to-minute changes in the availability of metabolic fuels. In pregnancy, ovarian steroids dramatically affect the ingestion, partitioning, and utilization of metabolic fuels. The detectors of metabolic fuel availability are under intense investigation. The sympathoadrenal system, which responds to hypoglycemia, and the central and peripheral sensors, which control food intake, are potential candidates. Evidence is mounting that leptin may serve as a detector of long-term metabolic fuel availability, signaling the presence of sufficient maternal fat stores to initiate reproduction.

Leptin has been implicated in the maturation and regulation of the reproductive system. Leptin treatment of *ob/ob* mice, which have a congenital deficiency of leptin and are infertile, stimulates the hypothalamic-pituitary-gonadal axis (32) and initiates pregnancy (33). Leptin also increases the serum concentrations of luteinizing hormone and ovarian and uterine weights in female mice. It is speculated that low leptin concentrations in women with extremely low body fat lead to infertility because of insufficient gonadotropin secretion (34). Elevated leptin concentrations in obese women do not adversely affect gonadotropin concentrations but may directly inhibit estrogen production by ovarian theca and granulosa cells and contribute to fertility problems.

Serial measurements of leptin throughout pregnancy have shown that serum leptin concentrations peak at 22–27 wk at $\approx$30 μg/L and then decline to 25.2 μg/L at 34–39 wk of gestation (35). Serum leptin per unit weight or per unit fat mass is 1.7-fold higher in pregnant women at 36 wk gestation than postpartum (36). Serum leptin is positively correlated with fat mass during pregnancy and postpartum. The slope of the regression of serum leptin on fat mass does not differ from that during the postpartum period, but the intercept is shifted upward. Leptin is positively correlated with gestational weight gain, but not birth weight, as reported by others (35, 37). During pregnancy, factors in addition to fat mass must regulate the expression of the *ob* gene. Between pregnancy and 3 mo postpartum, a mean 6% reduction in fat mass is associated with a 61% decrease in leptin. The decrease in leptin is partially explained by the drop in insulin, but 80% of the variation remains to be explained. Reproductive hormones such as progesterone, estrogen, and HCS are likely involved (38). It is now recognized that the placenta is a source of leptin. Leptin production has been detected in placental trophoblasts and amnion cells from the uteri of pregnant women (39) and in the syncytiotrophoblast cells of the human placenta (40).

In pregnant women, changes in appetite, thermogenesis, and lipid metabolism may be regulated in part by leptin. Leptin is known to inhibit the release of neuropeptide Y, a potent appetite stimulant. The elevated concentrations of leptin during pregnancy seem paradoxical, because presumably food intake is increased. The elevated leptin concentrations may actually represent a state of leptin resistance. Although there has been much speculation, the functional role of leptin in human pregnancy has yet to be elucidated.

PRACTICAL IMPLICATIONS

In the management of women with GDM, treatment modalities aimed to improve insulin sensitivity may be useful. Changes in diet, exercise, and achievement of desirable gestational weight gain should be encouraged to improve insulin sensitivity.

Guidelines for daily energy intake to support a desirable gestational weight gain have been provided for women with GDM. The American College of Obstetricians and Gynecologists (ACOG) recommends energy intakes of 35–40, 30, 24, and 12–15 kcal/kg (146–167, 126, 100, 50–63 kJ/kg) current weight for women whose current pregnancy weights are $<$80, 80–120, 120–150, and $>$150% of ideal body weight, respectively (17). The American Diabetes Association (ADA) has published similar guidelines (41). Self-monitoring of glucose, daily checking of urinary ketones, and exercise to enhance insulin sensitivity are integral components of many programs for women with GDM. Insulin therapy is initiated if fasting blood glucose exceeds target blood glucose values. Many centers use the value of 5 mmol/L for fasting blood glucose or 7.2 mmol/L for 1-h postprandial glucose (41).

In our study of women with GDM, we measured 24-h total energy expenditure (TEE) in late pregnancy under the sedentary conditions of a room respiration calorimeter (21). TEE averaged 2266 $\pm$ 251 kcal/d (9481 $\pm$ 1050 kJ/d) or 25 $\pm$ 2 kcal (105 $\pm$ 8 kJ) $\cdot$ kg^{-1} $\cdot$ d^{-1}. The ratio of TEE to the basal metabolic rate (1.24) was low because of confinement. In another study of healthy pregnant women, free-living TEE averaged 2833 $\pm$ 465 kcal/d (11 853 $\pm$ 1946 kJ/d) or 39 $\pm$ 7 kcal (163 $\pm$ 29 kJ) $\cdot$ kg^{-1} $\cdot$ d^{-1} at 37 wk of gestation; the ratio of TEE to the basal metabolic rate was 1.63 (13). Assuming similar applications of free-living physical activity, the women with GDM (mean weight: 89.7 kg) would be expected to have values of TEE around 2900 kcal/d (12 134 kJ/d) or 32 kcal (134 kJ) $\cdot$ kg^{-1} $\cdot$ d^{-1}. The recommended energy intakes of the ACOG (17) and the ADA (41) would not cover the estimated daily energy expenditure of these overweight women.

Energy restriction has resulted in improved glycemic control in obese women with GDM (42, 43). Energy restriction to 1200–1800 kcal/d (5021–7531 kJ/d) was implemented in obese women with GDM (44). With the energy-restricted diets, the incidence of macrosomia was 6%, compared with 23% in untreated control subjects. Knopp et al (42) studied obese women with GDM prescribed diets of 2400 kcal/d (10 042 kJ/d), 1600–1800 kcal/d (6694–7531 kJ/d) (33% reduction), or 1200 kcal/d (5021 kJ/d) (50% reduction). Glycemic control improved with both energy-restricted diets, but ketonuria increased 2–3-fold with the 50% energy reduction. Potentially deleterious effects of ketonemia on fetal development and subsequent intellectual performance of the infant warrant avoidance of ketonemia (45). Intelligence quotient was inversely correlated with plasma concentrations of β-hydroxybutyrate and fatty acids, but not with concentrations of acetonuria

in the third trimester (45). Although maternal weight gain and fetal macrosomia may be reduced, the safety of energy restriction in the management of GDM has not been established, and thus, it is not recommended by the ACOG (17).

Specific recommendations for diet composition were not made for women with GDM. The ADA states that the percentage of carbohydrate in the diet is dependent on individual eating habits and that the effect on blood glucose and percentage fat depends on assessment and treatment goals (41). This position acknowledges the need for individualization of dietary treatment.

Several programs have successfully used diets composed of 40–50% carbohydrate, 20% protein, and 30–40% fat (46). The lower percentage of carbohydrate blunts the postprandial hyperglycemia. In one study, patients with diet-controlled GDM were randomly assigned to a low-carbohydrate diet (< 42%) or a high-carbohydrate diet (45–50% of energy) (47). Carbohydrate restriction improved glycemic control, decreased the insulin requirement, decreased the incidence of large-for-gestational-age infants, and decreased cesarean deliveries for cephalopelvic disproportion and macrosomia.

In other work, women with GDM were randomly assigned to treatment groups with either intensive dietary therapy or dietary therapy plus supervised exercise (48). An arm ergometer was used 3 d/wk, 20 min/session, for 6 wk. The subjects in the exercise group normalized their glycohemoglobin and fasting and postprandial glucose concentrations in response to a 50-g glucose test. Also, Bung et al (49) evaluated the efficacy of exercise in the treatment of GDM. Exercise on a recumbent bike (at 50% of maximal oxygen uptake for 45 min, 3 times/wk) maintained normoglycemia and obviated the need for insulin therapy.

On the basis of recent advances in carbohydrate metabolism during pregnancy, preventive measures should be aimed at improving insulin sensitivity in women predisposed to GDM. Further research is needed to elucidate the mechanisms and consequences of alterations in lipid metabolism during pregnancy.

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