Maternal and Fetal Carbohydrate, Lipid and Protein Metabolisms

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ABSTRACT

Fetal period is characterized by the rapid growth and maturation of tissues and organs. There are various alterations in carbohydrate, lipid and protein metabolisms in mother to provide nutrition to fetus. If something is wrong about these metabolisms in mother, this will indirectly affect fetus. So it is essential to elucidate the maternal and fetal carbohydrate, lipid and protein metabolisms in the management of a pregnant woman. Mild fasting hypoglycemia, postprandial hyperglycemia, hyperinsulinemia and increased peripheral insulin resistance are the characteristics of pregnancy. The fetus primarily depends on glucose as the energy source but can also use other substrates such as lactate, keto acids, amino acids, fatty acids and glycogen as energy sources. Proteins are needed as structural components. Alterations in lipid metabolism cause accumulation of maternal fat stores in the early pregnancy in order to enhance lipolysis in the late pregnancy providing glucose and amino acids for fetus while promoting usage of lipids as maternal energy source. Maternal energy metabolism affects fetal energy metabolism both in short and long terms. By the clarification of maternal and fetal energy metabolisms, it may be possible to predict and prevent some diseases of a newborn in the future.

Key words: Fetus, carbohydrate, lipid, protein.

INTRODUCTION

Fetal period is the intrauterine period between 12th gestational week and birth and it is characterized by the rapid growth and maturation of tissues and organs. Carbohydrate and lipid metabolisms in pregnancy provide us continuous supply of nutrients to the fetus in spite of maternal intermittent food intake (1). The fetus primarily depends on glucose as the energy source and obtains glucose from the mother through the placenta. There are various alterations in carbohydrate, lipid and protein
metabolisms in mother to provide nutrition to fetus. If something is wrong about these metabolisms in mother, this will indirectly affect fetus. For example maternal diabetes mellitus and hyperglycemia may cause hyperinsulinemia and macrosomia in fetus (2) or the newborn with intrauterine growth retardation may have decreased amount of hepatic glycogen and adipose tissue due to decreased supply of maternal glucose. This may affect the newborn after delivery if hypothermia and hypoxia may deplete energy reserves (3). So it is essential to elucidate the maternal and fetal carbohydrate, lipid and protein metabolisms in the management of a pregnant woman.

**Maternal carbohydrate metabolism**

In early pregnancy, glucose tolerance is normal or slightly improved (4) and basal glucose and insulin concentrations are not different from the prepregnancy period (5). A progressive increase in basal and postprandial insulin concentrations is seen with advancing pregnancy (6). Pregnancy is characterized by a progressive increase in nutrient-stimulated insulin responses in spite of minor deterioration in glucose tolerance, resulting in progressive insulin resistance (7). It is suggested that insulin action in late normal pregnancy is 50-70% lower than in non-pregnant women by the hyperinsulinemic-euglycemic glucose clamp technique and intravenous glucose tolerance test (4,5,8-10). The alterations in the levels of human chorionic somatomammotrophin, progesteron, cortisol and prolactin all have a role in these changes (1). Glucose production from the glycogen depots in the liver also contributes hyperglycemia (11). In pregnancy basal hepatic glucose production has been shown to increase by 16-30% to meet the increasing needs of fetus (5,12). In spite of progressive decrease in insulin sensitivity with advancing pregnancy, endogenous hepatic glucose production was shown to remain sensitive to increased insulin concentration in normal pregnancy (1). Mild fasting hypoglycemia, postprandial hyperglycemia and hyperinsulinemia (13) and increased peripheral insulin resistance (4) may also be observed in pregnancy.

**Fetal carbohydrate metabolism**

The placenta and fetal liver function to supply nutrients to the fetus for fetal metabolism and growth (14). Carbohydrate is supplied to the fetus mostly in the form of glucose and lactate (15). Lactate is supplied to the fetus by the uteroplacental tissues and fetus gets glucose mostly from mother through placenta and also by gluconeogenesis (15,16). Fetus uses nutrients for the continuation of fetal oxidative metabolism, growth and maturation of tissues and organs. Fetal oxidative metabolism can be determined by oxygen usage and production of carbon dioxide (14). It is difficult to estimate production of carbon dioxide because of the huge difference between carbon usage and expulsion of rapidly growing fetus (14). Methodological advances in kinetic studies by using stable isotopic tracers and mass spectrometric quantification provide us better understanding of fetal energy metabolism (17).

Fluctuations in maternal blood glucose are reflected to fetal glucose concentrations. Glucose passes through the placenta without using energy by facilitated diffusion (18,19) and fetal glucose concentration is the 70-80% of maternal glucose concentration (20). The facilitated glucose diffusion is mediated by glucose transporters (GLUT) and GLUT 1, the dominant isoform in most fetal tissues and the placenta, is the rate limiting step of glucose transport (21). GLUT 1 in the placenta are saturated at glucose levels of 198-235 mg/dl (22), which may be a protective mechanism for the fetus (23). Although uterine, placental and fetal glucose uptakes are related to maternal glucose concentrations, the distribution of uterine glucose uptake to fetal and uteroplacental glucose uptakes is regulated by fetal glucose concentrations independent of the maternal glucose levels (20). The rates of umbilical uptake and utilization of glucose did not change with gestational age when they were evaluated on a weight specific basis in piglets (24). A fetus uses 55 kcal/kg/day based on calculation of fetal oxygen consumption (25). Fetus gets 80% of energy consumption from carbohydrates and fetal glucose utilization rate is higher in fetus than in adults (5-7 mg/kg/min vs 2-3 mg/kg/min) (23). Endogenous insulin has an essential role in the regulation of glucose metabolism in late gestation (26). Leptin has a role in the formation of neural pathways that are needed for the control of gluconeogenesis and tissue maturation in the late pregnancy (27).

The fetus can also use other substrates such as lactate, keto acids, amino acids, fatty acids and glycogen as energy sources (28). But gluconeogenesis and ketogenesis are not seen in the fetus when substrate supply is adequate (23). Normally fetus can not perform hepatic gluconeogenesis, and hepatic gluconeogenesis begins in the newborn period by the effects of thyroid, cortisol, and catecholamines (29). But gluconeogenesis can be seen in fetus by maternal starvation, prolonged hyperglycemia in mother and by cAMP infusion in fetus (29).
Maternal lipid metabolism

Carbohydrate and lipid metabolism are in close relationship with each other. Increased estrogen, progesteron and plasental lactogen increase levels of triglycerides, lipid, lipoproteins and apolipoproteins (30). Low density lipoprotein reaches its peak value by the 36th gestational week but decreases before birth. The level of high density lipoprotein is the maximum at the 25th gestational week and has a tendency to decrease by insulin resistance to the 32th gestational week (31). Cholesterol is used by the placenta for steroid hormone synthesis and fatty acids are used for placental oxidation and membrane formation (1). High density lipoprotein stimulates human placental lactogen through its receptors on the placenta (32). Lipids, lipoproteins and apolipoproteins decrease at various rates in the postpartum period also by the contribution of lactation (32). Alterations in lipid metabolism cause accumulation of maternal fat stores in the early pregnancy in order to enhance lipolysis in the late pregnancy by human chorionic somatomammotrophin. This provides glucose and amino acids for fetus while promoting usage of lipids as maternal energy source (1).

Fetal lipid metabolism

Glucose is the primary substrate for energy production in fetus but fetus can use other energy sources like lactate, keto acids, amino acids, fatty acids and glycogen under special conditions (23). Glycerol and certain free fatty acids pass through the placenta but triglycerides can not (23,33). Placental lipid transport to the fetus also involves lipid uptake from lipoproteins, metabolic alteration in the placenta, and release into the fetal plasma (16). Placental lactogen increases levels of free fatty acids by its lipolytic effects (31). Fetal fat accumulation occurs especially in the last trimester of pregnancy by the placental transfer of glucose and by its use as a lipogenic substrate and also by the placental transfer of fatty acids (33). Fatty acids are necessary not only as structural components but also for energy and metabolism. Amino acids are especially preferred for growth and essential fatty acids are especially used for development of brain and retina (23). Maternal glycerol is preferred to be used for gluconeogenesis instead of amino acids (23,36). Maternal ketone bodies can pass through the placenta and can be used by fetus as an energy source (33). Linoleic and linolenic acids are essential in the growth and maturation of fetal brain (34). It is suggested that maternal supplementation of a polyunsaturated fatty acid, docosahexaenoic acid may improve fetal neurodevelopment (35). In early pregnancy, fetal lipids are derived from maternal free fatty acids and in advanced pregnancy there is also synthesis in the fetal tissue (23,36). Lipogenesis is very active in the fetus and the increased maternal nutrition in late gestation uniquely enhances brown fat development which is important in conservation of heat and energy (37).

Maternal protein metabolism

Fetus gets amino acids mostly from the mother through the placenta and the passage of amino acids is critical since amino acids are the structural components of the fetus. There is a total of 1000 gram protein increase throughout the pregnancy and half of this belongs to the fetus and the fetoplacental tissues (32). Maternal serum albumin decreases and globulin increases in pregnancy. Placental lactogen and human chorionic gonadotrophin suppress deamination in the liver to prevent loss of amino acids to preserve amino acids for fetus (32). If mother gets insufficient carbohydrates and lipids, proteins are used as the energy source which is an undesirable condition. Insufficient maternal protein intake may also affect the disease susceptibility of the newborn in the future (38). In rats on a low protein diet, there was a significant decrease in the protein concentration and a significant increase in the glycogen concentration in the livers of their offsprings indicating the maternal insufficient protein intake not only reduced fetal growth but also altered the structure of the liver (38).

Fetal protein metabolism

Fetus needs 10 essential amino acids and cysteine, histidine and taurine. Ammonia produced by placenta is used by the liver for protein synthesis. Placenta can also produce some aminoacids like glutamate and aspartate (23). Fetal amino acid concentration is usually higher than maternal levels (39). Amino acids pass through the placenta by active transport by Na+/K+ - ATPase and H+-dependent transport. Protein molecules like albumin and gamma globulin pass to the fetus by pinocytosis (28). Active transport of amino acids may be either via accumulative transporters or exchangers. The accumulative transporters increase intracellular amino acid concentrations against concentration gradient, usually by cotransporting extracellular sodium (40) and exchangers change the intracellular amino acid composition by exchanging amino acids between the intracellular and extracellular compartments (40,41).
Fetus needs proteins as structural components and glucose as an energy source. Glucose and amino acid metabolisms interact with each other. Fetus tries to keep energy metabolism stable and in conditions with insufficient energy supplies, fetus may drop growth (20). In only prolonged energy and protein restriction, protein synthesis is affected to an important extend (42,43). The interaction of maternal and fetal energy metabolism. Maternal energy metabolism closely affects fetus in several ways. Maternal undernutrition causes low birthweight fetuses with increased risk of energy balance disorders (44). Maternal nutrition during pregnancy may also affect intrauterine development of body composition. Fetal abdominal fat was highest with low protein maternal diet; and fetal midthigh fat was highest at intermediate protein, high fat, and low carbohydrate diets (45). Maternal hypothyroidism may cause glucose intolerance and may contribute to the increased risk of type 2 diabetes in the offspring in rats (46). Gestational diabetes mellitus alters neonatal plasma lipids metabolism and causes hypercholesterolemia in the newborn period (47). Alterations in fetal development and growth have been associated with lifelong adverse health problems (48). Intrauterine growth restriction increases low-density lipoprotein cholesterol in rats and the fructose diet which is used as an enhancer of metabolic syndrome causes hypertriglyceridemia and hyperinsulinemia and decreased fasting glucose levels in rats (49). In rats maternal fructose intake during pregnancy causes maternal hyperglycemia and up-regulates hepatic sterol regulatory element-binding protein-1c expression in fetuses and in dams; leading to defects in carbohydrate and lipid metabolism in the adult offspring (50). Pregnant rats exposed to hypoxia demonstrated decreased fetal body and liver weight and it is suggested that prenatal hypoxia has a role in metabolic changes that enhances fetal vulnerability for nonalcoholic fatty liver disease, probably via insulin signaling pathway and glucose transporters (51).

Hormones are also critical in the regulation of energy metabolism. Insulin, insulin-like growth factor and thyroid hormones have anabolic effects on cellular nutrient uptake and production of energy; and leptin has a role in development of specific fetal tissues and glucocorticoids inhibit growth in utero (52). The fetus exposed to sustained hypoglycemia may have maintained hepatic insulin action in contrast to fetuses being exposed to placental insufficiency (53). Fetal sheep with intrauterine growth restriction have increased hepatic glucose production that is not suppressed by insulin; and cortisol and norepinephrine concentrations were positively correlated with glucose production rates (54). Maternal energy metabolism affects fetal energy metabolism both in short and long terms. By the clarification of maternal and fetal energy metabolisms, it may be possible to predict and prevent some diseases of a newborn in the future.

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