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Metabolic Changes in Diabetic Pregnancy

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During pregnancy, changes in carbohydrate, amino acid and lipid metabolism occur to ensure the continuous supply of nutrients to the fetus despite intermittent maternal food intake. While adaptations of carbohydrate and amino acid metabolism in pregnancy are reasonably well known, alterations in lipid physiology and their significance for fetal growth are still little understood. The purpose of this chapter is to review the overall metabolic changes that take place in pregnancy under normal and diabetic conditions, with special attention being given to those related to lipid metabolism.

Changes Occurring in the Mother during Pregnancy Affecting Fetal Growth

The continuous supply of metabolites derived from the maternal circulation, across the placenta, sustain fetal development. Whereas the most abundant nutrient crossing the placenta is glucose, followed by amino acids, the transfer of lipid components is limited [1]. However, lipids play a major role in fetal development, as shown by changes in their availability, such as those produced by variations in dietary fat composition, which are known to have major implications on fetal and postnatal development [2]. In addition, deviations from normal maternal plasma lipid status, such as hypercholesterolemia, can trigger pathogenic events in the fetus and may influence atherosclerosis later in life [3].

During the first two thirds of pregnancy the mother develops hyperinsulinemia and normal or even enhanced insulin sensitivity [4, 5], which in combination with hyperphagia and limited fetal growth allows her to store a large proportion of the nutrients she eats causing an accumulation of fat stores. During the last

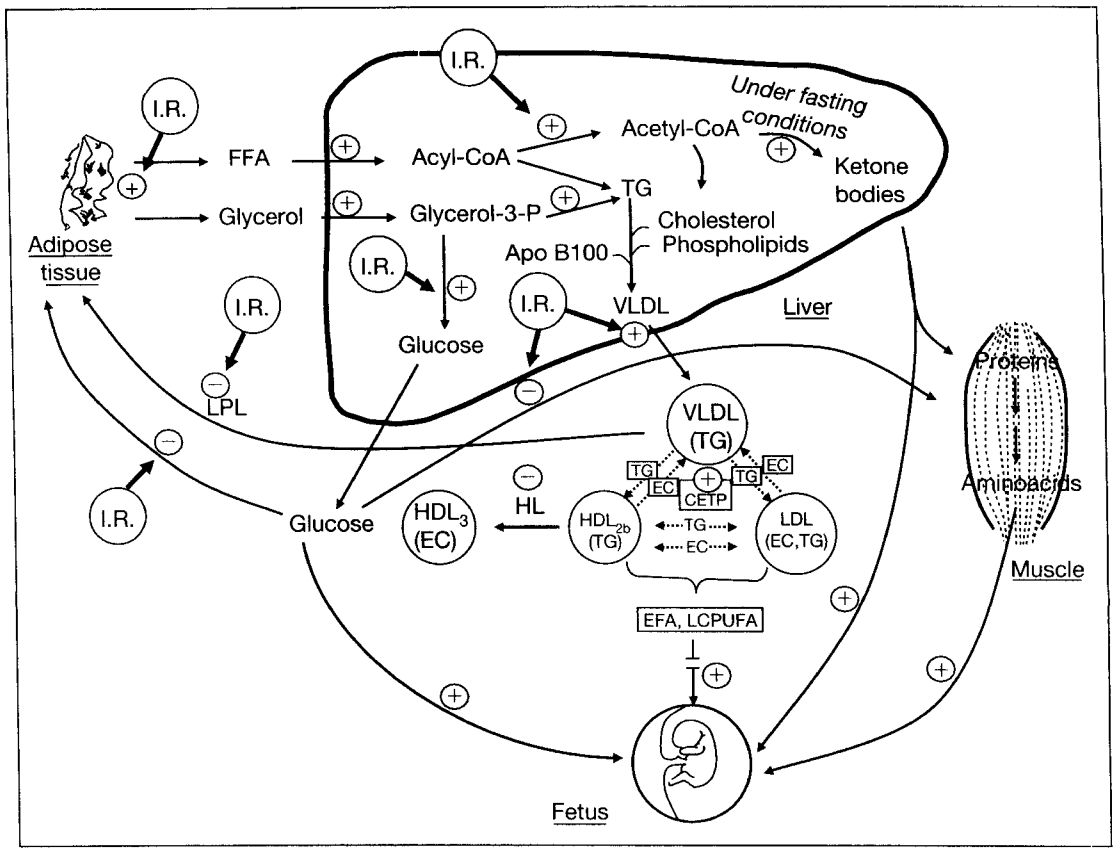

Fig. 1. Schematic representation of major interactions of maternal metabolism during late pregnancy with special emphasis on lipid metabolism and with indication of their consequences for the availability of substrates to the fetus and the controlling role of insulin resistance (I.R.). + = Activated steps; − = inhibited steps; TG = triacylglycerols; EC = esterified cholesterol; CETP = cholesterol ester transfer protein; EFA = essential fatty acids; LCPUFA = long-chain polyunsaturated fatty acids.

third of gestation the mother switches from the previous anabolic condition to a catabolic one permitting an enhanced transfer of nutrients through the placenta to sustain the rapid fetal growth. This catabolic condition is enhanced under fasting conditions, and is specially noticed in terms of an enhanced breakdown of lipid stores by lipolysis in adipose tissue, and is facilitated by the development of an overt insulin-resistant condition [6] (fig. 1).

Poorly controlled diabetes during the first 7 weeks of human pregnancy has been associated with a spectrum of developmental abnormalities including pre-implantatory embryo loss, increased resorption rate, induction of congenital anomalies, and embryonic developmental and growth delays. Although the mechanism of these effects in humans remains unknown, laboratory studies from diabetic animals have implicated maternal hyperglycemia as the principal teratogenic agent. Several closely interrelated pathways have been shown to be involved in the molecular mechanisms of hyperglycemia-induced tissue

damage: overproduction of reactive oxygen species, activation of protein kinase C isoforms, alteration in arachidonic acid metabolism leading to altered prostaglandin and nitric oxide production, increased hexosamine pathway flux, enhanced formation of advanced glycation end products and increased polyol formation.

Distinct from the impaired development that results from poorly controlled diabetes during early pregnancy, events occurring as a result of poor control during the latter two thirds of gestation include accelerated fetal growth and a risk of large-for-gestational age infants, respiratory distress syndrome, neonatal hypoglycemia, neonatal hypocalcemia and neonatal hypomagnesemia. It was initially proposed that overgrowth of the fetus in maternal diabetes was the result of increased delivery of glucose to the fetus, which consequently develops premature maturation of pancreatic insulin secretion, and subsequent hyperinsulinemia which together with the excess availability of glucose results in overgrowth of the fetus [7]. Formerly, it was proposed that overgrowth of the fetus of the diabetic mother was the result of the integrated impact of multiple maternal nutrients on fetal development [8]. Reports relating birth weights in diabetic pregnancies to maternal amino acid levels and maternal triacylglycerol levels support the view that fetal growth is controlled by several metabolic factors, maternal glucose being one of them.

Carbohydrate Metabolism

Glucose is the primary energy source of fetoplacental tissues. Under normal conditions, during early pregnancy, basal glucose and insulin concentrations do not differ from nongravid values [9], and hepatic gluconeogenesis is unchanged [10]. However, during late pregnancy the mother tends to develop hypoglycemia, which is especially evident during fasting. Indirect studies in women [11] and direct experiments in rats [12] have shown that the rate of gluconeogenesis is enhanced during pregnancy under fasting conditions, the effect being especially manifest when glycerol is the studied substrate [13]. Thus, gestational hypoglycemia occurs despite the enhanced gluconeogenesis and decreased consumption of glucose by the insulin-resistant tissues (fig. 1), and is therefore the result of enhanced utilization of glucose as a consequence of the high rate of placental transfer of glucose [14]. The placental transfer of glucose is carried out by facilitated diffusion according to concentration-dependent kinetics, being therefore dependent on the positive maternal-fetal glucose gradient, which is maintained by the low concentration of glucose in fetal circulation.

Carbohydrate metabolism has been studied in obese and nonobese women who were predisposed to and developed gestational diabetes mellitus (GDM) [15].

In longitudinal studies of lean women with GDM a progressive decrease in first-phase insulin response in late gestation was found, whereas first-phase insulin response in obese women developing GDM did not change but second-phase insulin response to intravenous glucose challenge increased [16]. Basal glucose production increases similarly in patients with GDM and in control subjects throughout gestation, but in late pregnancy insulin suppression of hepatic glucose production is less in GDM patients than in controls. It was found that in women with insulin-treated GDM at 32–36 weeks of gestation the total energy expenditure, basal metabolic rate, whole-body net carbohydrate and exogenous (dietary) glucose oxidation did not differ from control subjects [17]. Basal glucose concentrations decrease with advancing gestation in women developing GDM, and although at late gestation they have increased fasting insulin levels and decreased hepatic insulin sensitivity, hepatic glucose production was found either increased or unchanged in women with GDM compared to control women. Endogenous hepatic glucose production was shown to remain sensitive to increased insulin concentration in normal pregnancy, but was less sensitive in GDM [10]. In overweight patients with GDM, similar rates of fasting glucose appearance are achieved, but with elevated insulin concentrations relative to pregnant control subjects [18]. Total energy expenditure, basal metabolic rate and whole-body glucose utilization did not differ between insulin-treated GDM patients and controls [17].

Amino Acid Metabolism

The accretion of protein is essential for fetal growth, and nitrogen retention and protein synthesis are increased in pregnancy in both maternal and fetal compartments [19]. Nitrogen balance is improved and dietary protein is used more efficiently in late pregnancy [20]. A decrease in most maternal amino acid concentrations occurs both during early pregnancy, before the accretion of maternal or fetal tissues, and during late pregnancy. Since insulin infusion in healthy adults decreases both plasma amino acid levels and protein breakdown, the decrease in plasma amino acid levels and the lower rate of appearance of leucine found during normal pregnancy [21] indicate that the pregnancy-associated resistance to insulin does not involve muscle protein breakdown. There are also studies in which a decreased insulin sensitivity manifested by a decreased suppression of leucine turnover during insulin infusion in late normal pregnant women, and an increase in basal leucine turnover in women with GDM were found [15]. Studies of protein metabolism in fasted pregnant diabetic subjects been have shown to have normal [18] or higher rates of protein breakdown and oxidation but protein synthesis rates similar to normal pregnant

subjects [22], whereas well-controlled type 1 diabetes was found to cause no abnormalities in protein breakdown, synthesis or oxidation [23]. Plasma levels of branched chain amino acids (leucine, isoleucine, and valine) were found to be higher in GDM women during late pregnancy, whereas no change was found in several other amino acids (aromatics, phenylalanine and tyrosine, and proline). Also, there were others like glycine and threonine that were found to be lower in GDM than in normal control women. Although quantification of leucine and phenylalanine kinetics using stable isotope-labeled tracers showed no difference between GDM and control subjects [18], there are reports showing a higher rate of leucine nitrogen turnover in GDM women compared to normal subjects [24]. All of this suggests a significant alteration in maternal protein and amino acid metabolism in GDM women.

Distinct from glucose, the concentration of amino acids in fetal plasma is even higher than that found in the mother, because placental transfer of amino acids is carried out by an energy-dependent process, using selective transporters. This ensures the appropriate availability of these essential precursors to the fetus and may actively contribute to the tendency to maternal hypoaminoacidemia. Amino acids have a greater effect than glucose in stimulating fetal insulin secretion, and therefore changes in their delivery to the fetus may have profound consequences on fetal growth. The transport of neutral amino acids, which is mediated by the system A amino acid transporter, across the syncytiotrophoblast microvillous plasma membranes from placentas of women with diabetes has been shown to be either not affected [25], decreased [26] or even increased [27]. The uptake of leucine, but not of lysine or taurine was found increased in microvillous plasma membranes from placentas of GDM but not in those from type 1 diabetic women [27]. Most of these changes did not correlate with infant size, suggesting that they are not the primary cause for accelerated fetal growth in diabetic pregnancy.

Maternal Lipid Metabolism

Accumulation of lipids in maternal tissues as the result of major changes in adipose tissue metabolism and the development of maternal hyperlipidemia are the two most characteristic features of lipid metabolism during pregnancy.

Adipose Tissue Metabolism

Fat accumulation during pregnancy takes place during the first two thirds of gestation and occurs in both women [28] and experimental animals [29]. Body fat accumulation during early pregnancy appears to be the result of both hyperphagia and enhanced lipid (fatty acid and glyceride glycerol) synthesis in

adipose tissue [14], and is driven by the enhanced adipose tissue insulin responsiveness found in this early stage of pregnancy [2].

The accumulation of maternal fat stops during the last third of gestation as a consequence of enhanced adipose tissue lipolytic activity. Increased lipolysis of adipose tissue fat stores occurs in both women and rats during the last third of gestation, the change being especially manifest under fasting conditions [30–32].

The products of adipose tissue lipolysis, free fatty acids (FFA) and glycerol, are released, in large part, into the circulation. Since the placental transfer of these products is quantitatively low [1], their main destination is the maternal liver where, after conversion into active forms, acyl-CoA and glycerol-3-phosphate, respectively, they are partially reesterified for the synthesis of triacylglycerols that are released into the circulation as part of very low density lipoproteins (VLDLs). In addition, glycerol may be used for glucose synthesis and FFA for β-oxidation to acetyl-CoA leading to energy production and ketone body synthesis; these pathways also increase markedly under fasting conditions in late pregnancy [12, 33].

Since insulin inhibits adipose tissue lipolytic activity, hepatic VLDL secretion, gluconeogenesis and ketogenesis, the insulin-resistant condition of late pregnancy contributes to the increased adipose tissue lipolysis and the increased hepatic VLDL production, gluconeogenesis and ketogenesis at late pregnancy under fasting conditions (fig. 1). Furthermore, since the underlying pathophysiology of GDM is a function of decreased maternal insulin sensitivity or increased insulin resistance, those pathways become further enhanced in this condition, explaining the increase in plasma FFA and ketone bodies consistently seen in diabetic pregnancy [34, 35].

Maternal Hyperlipidemia

Enhanced maternal adipose tissue lipolytic activity during late gestation is associated with hyperlipidemia, mainly corresponding to increases in triacylglycerols, with smaller rises in phospholipids and cholesterol in the circulation. The greatest increase in plasma triacylglycerols corresponds to VLDL and results from enhanced production by the liver and decreased removal from the circulation as a consequence of reduced adipose tissue lipoprotein lipase (LPL) activity [36].

During normal pregnancy there is also an enrichment of triacylglycerols in other lipoprotein fractions that do not normally transport them, like low density lipoproteins (LDL) and high density lipoproteins (HDL) [36]. The abundance of VLDL triacylglycerols in the presence of an increase in cholesteryl ester transfer protein (CETP) activity which takes place at mid gestation contributes to this accumulation of triacylglycerols in LDL and HDL [37] (fig. 1). A further factor contributing to this effect is the decrease in hepatic lipase activity which

also occurs during late pregnancy [36], decreasing the conversion of buoyant HDL_{2b} triglyceride-rich particles into small HDL_3 triglyceride-poor particles, allowing a proportional accumulation of the former [36].

Both the insulin-resistant condition and the higher concentration of estrogen are thought to be responsible for the hypertriacylglycerolemia of pregnancy. As commented above, the insulin-resistant condition contributes both to the enhanced adipose tissue lipolytic activity which speeds up the transport of glycerol and FFA to the liver and their subsequent conversion into circulating VLDL triacylglycerols, and to the decreased LPL activity [38]. The increase in plasma estrogen concentrations during gestation also contributes to maternal hypertriacylglycerolemia since it enhances hepatic production of VLDL [39] and decreases the expression and activity of hepatic lipase [40].

Although exaggerated hypertriacylglycerolemia and lower LDL and HDL cholesterol have been found in diabetic pregnancy, there are reports which show no change in the maternal lipoprotein profile [34] or even decreased triacylglycerol levels [41]. Neither differences in the type of diabetes, degree of metabolic control or even the time of pregnancy studied explains this different response. As commented above, besides insulin resistance, hyperlipidemia occurring during gestation under normal conditions is driven by the increases in steroid hormones. Since plasma levels [34] as well as the level of sex hormone binding globulin [42] have been found decreased in diabetic women during early pregnancy or in those women in whom GDM subsequently developed, it is proposed that the degree of metabolic control and sex hormonal dysfunction may determine the development or lack of development of dyslipidemia in diabetic pregnant women, and this could explain the variety of reported findings.

Placental Transfer of Lipid Metabolites

Although triacylglycerols circulating in plasma lipoproteins do not directly cross the placental barrier [1], essential fatty acids from maternal diet, which are mainly transported as triacylglycerols in triacylglycerol-rich lipoproteins in maternal plasma [43], must be made available to the fetus. The presence of VLDL/apo E receptor, LDL receptor-related proteins and HDL receptors in placental trophoblast cells allow these lipoproteins to be taken up by the placenta. In addition, the trophoblasts also express different lipolytic activities including LPL, phospholipase A_2 and an intracellular lipase. Thus, maternal triacylglycerols in plasma lipoproteins are either taken up intact through the placenta receptors or, after hydrolysis, their constituent fatty acids are taken up by the placenta, where the fatty acids are reesterified to synthesize glycerolipids to provide a reservoir of fatty acids. Subsequent intracellular hydrolysis of the glycerolipids releases fatty acids that diffuse to fetal plasma.

Although smaller in proportion to lipoprotein triacylglycerols, maternal plasma FFA are also an important source of polyunsaturated fatty acids (PUFA) for the fetus. In human placenta there is a membrane fatty acid-binding protein ($FABP_{pm}$) [44] which is responsible for the preferential uptake and transfer of certain PUFA: docosahexaenoic > α-linolenic > linoleic > oleic > arachidonic acid [45]. The selective uptake of certain fatty acids may also contribute to a degree of selective placental metabolism such as their conversion to prostaglandins and other eicosanoids, the incorporation of some fatty acids into membrane phospholipids, fatty acid oxidation and fatty acid synthesis. The combination of all these processes determines the actual rate of placental fatty acid transfer and its selectivity, resulting in the proportional enrichment of certain PUFA, such as arachidonic acid and docosahexaenoic acid, in the fetal compartment compared to the maternal compartment.

Placental transfer of maternal cholesterol has been shown to be effective in different species, such as rat, guinea pig and rhesus monkey. Cholesterol synthesis in fetal tissues has also been shown to be highly active in some species. In humans, the comparison of maternal plasma concentrations of lipoprotein cholesterol and those in umbilical cord blood cholesterol gave positive correlations in some studies [46] but no correlation in others [47]. Gestational age seems to influence these comparisons, since in fetuses younger than 6 months, plasma cholesterol levels significantly correlate with the maternal ones [48], suggesting that, at these early stages of gestation, maternal cholesterol actively contributes to fetal cholesterol. At term, although there is delivery of cholesterol from placenta to the fetus, its contribution to the fetal plasma cholesterol pool is minor, and endogenous cholesterol synthesis appears to be the principal source of fetal cholesterol.

Although intrinsic changes in placental capability to lipid transfer in diabetic women cannot be discarded, altered lipid profile on the maternal side affects the quantity and/or quality of lipids being transferred to the fetus. In fact, maternal dietary fatty acids influence fetal lipid metabolism and contribute to postnatal metabolic changes [2, 49]. GDM patients with macrosomic fetuses have been associated with high triglyacylglycerol, VLDL and HDL triacylglycerol levels [50]. Besides, macrosomic newborns of poorly controlled diabetic mothers have higher lipid and lipoprotein lipid levels than those found in controls [51], and levels of cholesterol, phospholipids and triacylglycerols in umbilical cord were found enhanced and correlated with FFA in fetuses of type 1 diabetes mellitus (DM) mothers [52]. The increased concentration of FFA in fetal blood of type 1 DM pregnancies is probably caused by increased delivery from maternal circulation, because an increased maternofetal gradient has been reported in diabetes [53]; this may drive the synthesis of cholesterol, triacylglycerols and phospholipids in the fetus of type 1 DM mothers. Moreover, the

placental transport of triacylglycerol fatty acids may be exaggerated in diabetes, where LPL declines in adipose tissue, contributing to maternal hypertriacylglycerolemia, but not in placenta [54].

During the perinatal period, maternal supplies of arachidonic acid and docosahexaenoic acid are the likely major sources of long-chain PUFAs to the fetus. Despite the same proportion of phospholipid arachidonic acid and docosahexaenoic acid in control and GDM women, fetal erythrocyte phospholipid arachidonic acid and docosahexaenoic acid are lower in women with GDM than in control subjects [55], suggesting an impairment in the maternal transfer of these fatty acids to the fetus.

Conclusion

The continuous supply of metabolites derived from maternal circulation, across the placenta, sustains fetal development. Under normal conditions, during the first two thirds of gestation, the mother develops hyperinsulinemia and normal or enhanced insulin sensitivity, contributing to an accumulation of fat stores. During the last third of gestation the mother switches to a catabolic condition, which is facilitated by her insulin-resistant condition and accelerates the availability of nutrients across the placenta. Poorly controlled diabetes during the first 7 weeks of human pregnancy has been associated with a spectrum of abnormalities in embryonic development, including embryo loss, induction of congenital anomalies and growth delay, maternal hyperglycemia being the principal teratogenic agent. However, poorly controlled diabetes during the latter two thirds of gestation accelerates fetal growth, and induces large-for-gestational age infants, respiratory distress syndrome and neonatal hypoglycemia. Studies on carbohydrate metabolism have shown that insulin suppression of hepatic glucose production is less decreased in GDM patients than in controls. An increase in basal leucine turnover and increased plasma branched amino acid levels were also found in GDM women at late pregnancy, suggesting a significant alteration in maternal protein and amino acid metabolism. Since enhanced adipose tissue lipolysis and liver production of VLDL triacylglycerol and decreased extrahepatic LPL activity during late pregnancy are caused by the insulin-resistant condition, a further decrease in insulin sensitivity in pregnant diabetic women would accelerate these changes and exaggerate the development of maternal hypertriacylglycerolemia. Since increased estrogen concentrations in late pregnant women actively contribute to the enhanced liver production of VLDL triacylglycerol, the decreased estrogen levels found in pregnant diabetic women may counteract such a change, avoiding the development of such exaggerated hypertriacylglycerolemia in certain diabetic subjects. These changes in maternal

metabolism together with alterations in intrinsic placental function affect the quantity and quality of nutrients reaching the fetus, and consequently contribute to altered fetal growth.

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