Metabolic Adaptations in Pregnancy: A Review

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Keywords

Metabolic adaptations · Pregnancy · Fetus

Abstract

Background: Pregnancy is a dynamic state involving multiple adaptations that are necessary in order to ensure a continuous supply of essential metabolites to support the growth and the development of the fetus. **Objectives:** This review article is aimed to discuss important adaptations in metabolism that take place during non-complicated pregnancy. **Materials and Methods:** We searched the electronic database PubMed for pre-clinical as well as clinical controlled trials reporting the importance of metabolic adaptations during a non-complicated pregnancy. The preferred language was English and the most recent reports were selected to get an updated review. **Results:** It was observed clearly in the searched literature that metabolic adaptations are a crucial part of pregnancy, as they provide the mother with sufficient energy stores to meet the demands of pregnancy. These adaptations also help in preparing the mother for lactation and also help in providing proper environment for the proper growth of fetus in the womb. Moreover, multiple biomolecules including glucose, fatty acids, ketone bodies, hormones collectively contribute toward these metabolic adaptations. **Conclusions:** This review article concludes that metabolic adaptations are crucial for proper fetus development.

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Introduction

Human pregnancy is characterized by alterations in maternal lipid metabolism, which could be divided into 2 phases: an anabolic phase and a catabolic phase [1, 2]. The anabolic phase occurs in the first 2 trimesters of human gestation and is attributed to several factors that cooperatively increase the deposition of lipids in maternal tissues [3]. The first factor is maternal hyperphagia, which progressively increases throughout gestation, thereby boosting the availability of exogenous metabolic substrates [4]. Enhanced de novo lipogenesis is another factor contributing to early pregnancy anabolism. Specifically, in situ studies in rat periuterine adipose tissue have demonstrated a progressively increasing conversion of glucose to fatty acids and glycerol glyceride until day 20 of rat pregnancy [5]. Moreover, it has been suggested that augmented lipoprotein lipase (LPL) activity could promote fat deposition in human as well as rat pregnancy by hydrolyzing both triglyceride-rich chylomicrons and very low density lipoproteins (VLDLs) circulating in plasma in order to release non-esterified free fatty acids/glycerol for adipose tissue uptake [6]. Furthermore, increased intracellular utilization of glycerol is a factor proposed to facilitate early pregnancy anabolism. In particular, under normal circumstances, the conversion of glycerol to glycerol-3-phosphate, an essential precursor for triglyceride biosynthesis, is minimal due to the negligible activity of the enzyme glycerol kinase [7]. Consequently, the

Fig. 1. Overview of metabolic adaptations during pregnancy.

decreased adipose tissue lipolytic activity together with the augmented capacity of maternal tissues to employ both glucose and intracellular glycerol for the production of glycerol-3-phosphate result in net triglyceride accumulation. Figure 1 shows the overall overview of metabolic adaptations during pregnancy.

Catabolic Phase

The switch to net catabolic state occurs in the third trimester of human gestation and is characterized with an accelerated breakdown of fat deposits as a consequence of enhanced adipose tissue lipolytic activity. Specifically, studies in late pregnant rats have demonstrated increased mRNA expression and activity of hormone-sensitive lipase in white adipose tissue [8]. Additionally, it has been shown that the levels and the activity of adipose tissue LPL are reduced in women and rats with late pregnancy [9], thereby decreasing the deposit of lipids in maternal adipocytes. Non-esterified fatty acids (NEFA) and glycerol are converted to acyl-CoA and glycerol-3-phosphate, respectively, by the liver; partial re-esterification is performed for the synthesis of triglycerides. The hepatic triglycerides are transferred to native VLDL particles and subsequently released into the maternal circulation.

Alternatively, glycerol could be used for glucose synthesis, while NEFA could be oxidized to acetyl-CoA for energy production as well as ketone body synthesis. These pathways are essential for the fetus development because during late gestation, requirements for metabolic substrates are greatly augmented. The preferential use of glycerol for gluconeogenesis acquires greater importance during maternal fasting periods later in pregnancy when essential gluconeogenic substrates are sparse while delivery of newly formed glucose is vital for the fetus [10]. Moreover, studies have shown that under fed conditions in early gestation, plasma ketone body levels are lower in pregnant than in non-pregnant rats, suggesting an enhanced utilization of this energy substrate [11]. Based on the fact that placental transfer of ketone bodies is highly efficient during periods of fasting, maternal ketogenesis becomes highly accelerated allowing the fetus to employ these molecules not only as energy fuels but also as substrates for brain lipid synthesis [12].

Hyperlipidemia of Pregnancy

Enhanced lipolytic activity in the adipose tissue of the mother in the third trimester of pregnancy precipitates the development of maternal hyperlipidemia, which

mainly corresponds to increases in plasma triglyceride levels, whereas the rise in cholesterol and phospholipid concentrations are less marked [13]. Triglycerides predominantly increase in VLDLs, but they also get enriched in other lipoprotein fractions that do not normally transport them, such as low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs). The activity of this protein peaks during the second trimester of human pregnancy and then declines in the third trimester, reaching its lowest point postpartum [14]. It has been suggested that the changes in CETP activity correlate with the alterations in HDL-triglyceride levels, which increase dramatically from the first to the second trimester of pregnancy. Moreover, hepatic lipase is responsible for converting buoyant triglyceride-rich HDL2 subfraction into small triglyceride-poor HDL3 particles and the reduced activity of this hydrolase during gestation allows enhanced proportional accumulation of triglyceride-rich HDL2 lipoproteins in the plasma of pregnant women.

Even though the molecular mechanisms contributing to gestational hypertriglyceridemia have been extensively studied, there is a substantial gap in our knowledge regarding the adaptations in the lipid metabolism of the mother that facilitate the rise in plasma total and lipoprotein-cholesterol levels during human pregnancy. Moreover, it is well established that unesterified cholesterol overload is cytotoxic and this has necessitated the evolution of complex regulatory mechanisms imposing stringent control on the intracellular levels of this sterol [15]. However, till now, there is no information on how maternal tissues are able to limit the internalization of the exogenous cholesterol that circulates abundantly throughout gestation. The pressing need to answer these questions is underscored by pregnancy conditions, for example, Smith-Lemli-Opitz Syndrome (SLOS) [16], gestational hypercholesterolemia, and hypocholesterolemia [17], where impaired cholesterol homeostasis during pregnancy has a detrimental effect on the development of the embryo in utero and thereby has a negative impact on its adult health. Fetal growth is directly dependent on the availability of maternally derived nutrients and the capacity of the placenta to transport these nutrients from the mother to the fetus. The placenta is an organ anatomically configured to prevent direct contact between maternal and fetal blood and, as a consequence, relies exclusively on facilitated diffusion, active transport against concentration gradients to drive electrochemical potential, and metabolite flux.

Glucose Transporters Role

Glucose is the primary energy source for the growth of the fetoplacental unit. The high demand for this substrate in combination with the minimal contribution of fetal gluconeogenesis necessitates the development of a rapid system for transfer of maternal glucose by facilitated diffusion (via glucose transporter [GLUT] proteins) along a concentration gradient (higher maternal glucose concentrations compared to fetal drive net glucose transport toward the fetus). The GLUT family comprises 14 isoforms of integral transmembrane proteins [18]. Even though many of these isoforms have been identified in human placental tissue, GLUT1 is considered the primary GLUT in human placenta based on the fact that it is the only one detected as a functional protein near term in the syncytiotrophoblast [19].

GLUT1 is asymmetrically distributed across the placenta, with a threefold higher prevalence of the transporter in the microvillous membrane than in the basal, suggesting that the rate-limiting step in trans-syncytial glucose flux occurs at the basal membrane [20]. Moreover, studies have also demonstrated that the overall GLUT1 expression increases during pregnancy; however, the levels of this transporter in the microvillous membrane remain unchanged during the late second and third trimesters of pregnancy, whereas its basal membrane expression increases by approximately 50% over the same period [21]. Moreover, it has been shown that the enhanced transport of glucose across the rate-limiting basal membrane in combination with a rise in uteroplacental and umbilical blood flow induce the substantial elevation in the supply of glucose to the fetus during the second half of pregnancy [22].

Role of Fatty Acids

Fatty acids play a critical role in fetal development and function as a key energy source; they are essential structural components of cellular membranes and precursors for bioactive signaling compounds; fatty acids are indispensable for fetal tissue development (e.g., white adipose tissue accretion) and organogenesis (e.g., brain development) [23]. Studies have demonstrated that placental LPL activity increases as gestation progresses and this lipase hydrolyses triglycerides in chylomicrons derived from diet as well as VLDLs [24]. On the other hand, HDL-triglycerides are a preferential substrate of endothelial lipase. The expression of endothelial lipase also changes

during pregnancy so that its mRNA levels are higher in term placentas than in first-trimester ones [25]. Fatty acid transport proteins (FATPs) are integral membrane proteins present in human placental membranes that mediate the preferential uptake of long chain polyunsaturated fatty acids (LCPUFA) into syncytiotrophoblast [26]. Even though human placenta expresses 5 out of the 6 members of the FATP family (FATP1–4, 6), FATP1 and FATP4 have been most extensively studied due to the fact that their expression correlates with docosahexanoic levels in maternal plasma, cord blood, and placental phospholipids, suggesting an important role of these isoforms in the transfer of LCPUFA [27]. Furthermore, within the cytosol of syncytiotrophoblasts, NEFAs are bound by fatty acid-binding proteins (FABPs) (human placenta has been shown to express 4 different isoforms of FABPs [FABP1, 3, 4, and 5]). These are trafficked to cellular sites for esterification, beta-oxidation, and subsequent transfer to the fetus [28]. Finally, NEFA that cross the syncytiotrophoblast are carried to the fetal liver in α -fetoprotein where they are re-esterified and released into the fetal circulation in the form of triglycerides [11]. However, it is still unclear as to which step in the process limits the rate of placental fatty acid transport to the fetus.

Importance of Cholesterol

Cholesterol plays a key role in embryonic and fetal development. It is an essential component of cell membranes where it determines membrane fluidity and passive permeability. This sterol also maintains cholesterol-rich microdomains called lipid rafts that are key for plasma membrane-dependent signaling cascades such as the sonic hedgehog pathway. Cholesterol is also a precursor for bile acids and steroid hormones (e.g., glucocorticoids that are actively synthesized in fetal adrenal during late pregnancy). Moreover, it plays important roles in cell proliferation, differentiation, as well as cell-to-cell communication. Cholesterol and its oxidative derivatives, oxysterols, are regulators of various metabolic processes. It has been estimated that there must be a net accumulation of approximately 1.5–2.0 g of cholesterol for each kg of tissue that is added to the body of the developing embryo [29]. As a consequence of its high demands for cholesterol, the developing fetus obtains this sterol either as a product of *de novo* biosynthesis or from maternally derived deposits of cholesterol in the yolk sac and the placenta [30]. There has been a debate as to whether human fetuses use cholesterol from the mother to support

their development or whether they rely entirely on their endogenously produced sterols. The most compelling line of evidence demonstrating that maternal cholesterol can be transported transplacentally to maintain the growth of the fetus comes from babies born with the congenital condition, namely, SLOS who are unable to synthesize cholesterol *de novo*. Specifically, fetuses harboring nonsense mutations in the gene encoding $\Delta 7$ -dehydrocholesterol reductase, the enzyme catalyzing the conversion of 7-dehydrocholesterol into cholesterol, are capable of developing to term and are born with low levels of the sterol in their tissues [31]. However, the exact mechanism for the removal of cholesterol from maternal circulation and its delivery to the fetoplacental unit remains unclear. Specifically, it has been shown that human placental trophoblasts express LDL receptor (LDLR), VLDL receptor, and scavenger receptor class B type I transmembrane proteins, which mediate the removal of cholesteryl esters from maternal plasma lipoproteins and help in their transfer to the fetal circulation [32]. Moreover, ApoE is another possible component of the maternal-embryonal cholesterol transport system. In particular, ApoE is a ligand involved in the transport and receptor-mediated uptake of lipoproteins by various cell types and it has several isoforms that differ in their lipoprotein receptor-binding affinities and consequently has profound effects on plasma cholesterol concentrations [33]. In humans, heterozygous mothers with an ApoE2 allele (protein isoforms defective in LDLR binding) have infants with a more severe SLOS phenotype as compared to mothers without the ApoE2 allele [34]. *Ex vivo* studies in placental biopsies have demonstrated that human placenta not only expresses ApoB and microsomal triglyceride transfer protein but also is able to synthesize and secrete ApoB-100-containing lipoproteins. These in turn could mediate the transport of cholesterol from the basal membrane to the fetus [35]. ABCA1 has also been recently identified as a gene whose variants in the mother significantly correlated with the severity of SLOS phenotype of the infant. This observation suggested that placental cholesterol transfer pathways are not only vital for fetal development but also present as a plausible target for prenatal SLOS therapy [36]. Furthermore, maternally derived cholesterol plays a role in the growth and the development of fetuses unaffected with SLOS. Specifically, low maternal serum cholesterol levels during pregnancy are associated with reduced birth weights. Also, low maternal serum cholesterol levels have a trend for raised incidence of microcephaly, while maternal gestational hypercholesterolemia promotes early atherogenicity [37].

Role of Ketone Bodies

Ketone bodies are essential oxidative substrates used as glucose substitutes to fuel the metabolism of both the mother and the fetus. As previously mentioned, their circulating levels in the mother are greatly increased under fasting conditions as a result of accelerated lipolysis and hepatic ketogenesis later in pregnancy. The transfer of ketone bodies across the placenta occurs either via un-facilitated diffusion down their concentration gradient or by beta-D-hydroxybutyrate placental carrier-dependent transport [38]. Unrestricted and rapid arrival of ketone bodies from the maternal to fetal circulation is an essential adaptation, which guarantees embryonic brain development under conditions of nutrient deficiency [39]. However, this adaptation could also have detrimental effects on fetal development, since extended periods of maternal hyperketonaemia have been associated with increased incidence of fetal malformations, impaired neurophysiologic development as well as still birth [40].

Amino acids play a critical role in embryonic development; therefore, their plasma concentrations are substantially higher in fetal than maternal circulation, indicating active transport of these peptides across the syncytiotrophoblast. Human placenta expresses over 15 different amino acid transporters and each one of them is responsible for the uptake of several different amino acids [41].

Contribution of Hormones to the Metabolic Adaptations during Pregnancy

The switch from net anabolic to net catabolic state throughout pregnancy has been attributed to alterations in the insulin sensitivity of the mother. During early pregnancy, the activity of the pancreatic beta cells is increased, as evidenced by the enhanced insulinotropic effect of glucose observed in both women and rats, while whole-body insulin sensitivity is unchanged or even augmented [42]. Consequently, it has been proposed that hyperinsulinemia in the first 2 trimesters of gestation is the principal factor promoting maternal lipogenesis and fat deposition. In contrast, the last trimester of gestation is associated with progressive insulin resistance, which is believed to cause the increase in adipose tissue lipolysis, hepatic gluconeogenesis, and ketogenesis [43].

Moreover, estrogen is a reproductive hormone, which increases progressively throughout pregnancy, and is a key factor contributing to the development of maternal hyperlipidemia as a means to ensure reproductive success

as well as proper fetal development. Specifically, it has been shown that estrogen enhances the production of light VLDLs and also reduces the expression and activity of hepatic lipase in the liver thereby, inhibiting the clearance of circulating triglyceride-rich lipoproteins. Moreover, studies in postmenopausal women undergoing hormone-replacement therapies have demonstrated that exogenously administered estrogens increase the levels of plasma HDL-cholesterol and triglycerides and reduce the concentrations of total cholesterol as well as LDL-cholesterol [44]. Also, estrogen is shown to increase insulin receptor binding in primary rat adipocytes, thereby possibly enhancing insulin sensitivity during pregnancy.

Progesterone is another key reproductive hormone whose levels escalate throughout gestation, although it exerts no significant effect on lipoprotein metabolism. Studies in premenopausal women administered with the progesterone-only pill have shown marginal reductions in the levels of circulating total cholesterol and triglycerides [45]. However, it has been suggested that the administration of progesterone derivatives is able to blunt the changes in serum lipid profiles due to estrogen [46]. The magnitude of these effects varies depending on the androgenic properties of the different progesterone derivatives; natural progesterone is not able to significantly modify estrogen-induced adaptations in lipoprotein profiles [47].

Furthermore, several placental hormones have been implicated in re-programming maternal physiology in order to achieve an insulin-resistant state. Human placental lactogen increases 30-fold throughout gestation and is shown to stimulate insulin secretion in human islets [48]. Moreover, studies in cultured rat adipocytes have suggested that while this hormone has no effect on insulin-receptor binding, it is able to interfere with post-binding glucose transport, thereby promoting insulin resistance.

Human placental growth hormone is a peptide that differs from pituitary growth hormone by 13 amino acids and it has also been implicated in promoting insulin resistance in late gestation. It is detectable in plasma from week 5 and its levels progressively rise throughout gestation effectively replacing pituitary growth hormone in the maternal circulation from mid-gestation onwards [49]. Moreover, transgenic mice overexpressing the human placental growth hormone gene become larger than their normal littermates and are hyperinsulineamic as well as insulin resistant [50]. Adipose tissue-secreted factors such as leptin and adiponectin have also been considered candidates actively mediating insulin resistance of preg-

nancy [51]. For instance, tumor necrosis factor alpha (TNF α) is a cytokine produced by various tissues including white adipose tissue and placenta [52]. There is an inverse correlation between the insulin sensitivity of women at different stages of pregnancy and the plasma concentrations of this pro-inflammatory factor [53]. Moreover, TNF α is recognized as a predictive marker of insulin resistance and its plasma levels are higher during advanced gestation in women with GDM than in women with non-complicated pregnancies [54]. Furthermore, there is evidence of impaired insulin receptor and IRS-1 tyrosine phosphorylation as well as increased serine phosphorylation in skeletal muscle indicating that TNF α could be a key hormonal factor mediating insulin resistance in human gestation [55].

Conclusions

It could be concluded from the above discussion that metabolic adaptations are crucial for the proper development of the fetus. Diverse biomolecules including glucose, fatty acids, cholesterol, ketone bodies, and hormones maintain proper balance in these metabolic adaptations during pregnancy. Any abnormality among these metabolic adaptations could seriously affect the development of the fetus.

Disclosure Statement

The authors declare no conflicts of interest.

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