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Maternal-fetal metabolism in normal pregnancy and preeclampsia

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1. ABSTRACT

Adaptation to pregnancy in humans involves major anatomic, physiologic and metabolic changes in the mother in order to support and provide for the nutritional and metabolic needs of the growing conceptus. Metabolically, pregnancy is marked by several important and dynamic adjustments including increased insulin resistance, hyperlipidemia and changes in protein and amino acid metabolism. In general, these metabolic adaptations serve to increase nutrient availability for the benefit of the growing fetal-placental unit. Interestingly, the pregnancy complication preeclampsia is recognized to evidence biologic exaggerations of these normal metabolic adaptations of pregnancy. Specifically, preeclampsia is associated with increased insulin resistance, hypertriglyceridemia, high circulating free fatty acids, low high-density lipoprotein particles, and high maternal and fetal plasma amino acid concentrations. These metabolic alterations may contribute to the pathophysiology of the syndrome and may also influence fetal growth. The focus of this review will be to summarize the normal metabolic adaptations, transport and utilization of carbohydrates, lipids and amino acids that occur during pregnancy. Furthermore, we will review the differences in carbohydrate, lipid and amino acid metabolism in pregnancies complicated by preeclampsia in comparison to uncomplicated pregnancies.

2. INTRODUCTION

Pregnancy is a metabolically dynamic state. There are two differentiated metabolic stages during pregnancy. The first stage corresponds to the first two thirds of pregnancy when fetal growth is limited and differentiation and organogenesis are dominant. During this first stage, maternal metabolism is anabolic and directed toward storing a greater proportion of accumulated nutrients, as evidenced by an accumulation of fat stores (1, 2). The second stage corresponds to the last third of pregnancy when fetal growth is rapid, and growth is supported by a maternal switch to catabolic metabolism and enhanced transfer of nutrients by the placenta. This second stage is partly reflected by an enhanced breakdown of lipid stores, and increased rates of ketogenesis and gluconeogenesis especially under conditions of reduced food intake (3-6). This metabolic balance is ideally designed to provide a continuous supply of nutrients for fetal and placental growth even under conditions in which maternal nutrient intake is suboptimal. This review will attempt to summarize the metabolic adaptations that take place during pregnancy as well as describe notable metabolic differences in pregnancies complicated by the pregnancy syndrome preeclampsia, including increased insulin resistance, hyperlipidemia and differences in maternal and fetal amino acids (Table 1). This review will focus in general on the key nutrients that have been investigated during pregnancy including glucose, lipids (triglycerides, free fatty acids,

Table 1. Summary of metabolic changes in pregnancy and preeclampsia.

	Normal Pregnancy		Preeclampsia	
	Early Anabolic	Late Catabolic	Early Anabolic	Late Catabolic
Maternal metabolism				
Glucose tolerance	~	↓	~↓	↓↓
Insulin sensitivity	~	↓	~↓	↓↓
Free fatty acids	↑	↑↑	↑↑	↑↑↑
Triglycerides	↑	↑↑	↑↑	↑↑↑
Cholesterol	~	↑	~↑	↑↑
Maternal amino acid oxidation	~	↓	?	?
Maternal amino acids	↓	↓	?	↑ compared to normal pregnancy
Fetal amino acids		↑ compared to maternal		↑ compared to normal pregnancy

~: similar compared to nonpregnant controls, ↑, ↑↑, ↑↑↑: elevated compared to nonpregnant controls, ↓, ↓↓: lower compared to nonpregnant controls, ?: unknown or incomplete information

glycerol), and amino acids. This is obviously a very partial list and does not address other important nutrients including micronutrients (calcium, sodium, iron, magnesium, etc.) and vitamins (please refer to recent reviews) (7-10).

2.1. Preeclampsia

Preeclampsia is a pregnancy-specific syndrome and a leading cause of maternal and fetal morbidity and mortality (11-13). Clinically, preeclampsia is diagnosed by a gestational increase in maternal blood pressure and proteinuria. However, preeclampsia is more than these basic clinical measures. The syndrome is discussed in greater detail by Roberts in this same issue. With regard to placental function and metabolism, preeclampsia is associated with shallow placentation and incomplete to failed spiral artery remodeling (14-16). The non-remodeled spiral arteries remain narrow with a responsive muscular wall and likely limit optimal blood flow necessary to sustain normal fetal and placental nutritional demands. In addition, preeclampsia is associated with several maternal metabolic changes including dyslipidemia with elevated triglycerides, free fatty acids, high LDL cholesterol, and lower HDL cholesterol (17). Insulin resistance and hyperuricemia are components of the metabolic syndrome and are also more common in preeclampsia (18-20). Many of these changes are evident before the onset of the syndrome later in pregnancy. The potential role of these components in relation to maternal-fetal interactions will be addressed in more detail below.

3. THE PLACENTA AND NUTRIENT TRANSPORT

The placenta plays a central role in nutrient transport between the maternal and fetal compartments. The placenta processes signals sent by the maternal and fetal organisms to regulate fetal demand and maternal substrate supply, ensure it's own metabolic demands and transfer fetal waste into the maternal circulation (Figure 1). During the embryonic period, organogenesis is the main goal and fetal growth is minimal. Implantation and the formation of the placenta is a highly coordinated process involving interactions between maternal and embryonic cells. Trophoblast cell invasion of uterine tissues and remodeling of uterine spiral arterial walls ensures that the developing feto-placental unit receives the necessary supply of blood, and that efficient transfer of nutrients and gases and the removal of wastes can take place. The

process of decidualization also enriches the nutrient environment for the conceptus, such that the maternal endometrium becomes rich in glycogen and lipids. The invading trophoblast create lacunae, which eventually expand and coalesce to become the intervillous space of the mature placenta which will be bathed in nutrient rich maternal blood and will surround the trophoblastic villi containing fetal vessels. This fetal-maternal interface allows efficient nutrient and waste exchange. The placenta grows across gestation, first by an increase in mass and then by an increase in surface area. The majority of nutrient transfer between the mother and the fetus occurs across the single layered syncytiotrophoblast. Nutrients reach the fetus from the maternal circulation that is in direct contact with the microvillous membrane of the syncytiotrophoblast. Nutrients then cross the basolateral membrane of the syncytiotrophoblast that is adjacent to the fetal capillary endothelium. However, this is an overly simplistic view of placental function, and ignores the fact that the placenta itself is also active metabolically (21, 22). For example, during late gestation the placenta itself may consume as much as 40-60% of the glucose and oxygen supplied by the uterus (22). In addition, nutrients are also metabolized by the placenta and may generate energetic intermediates for the production of alternative fetal fuels.

Much of what is known about human placental transport is derived from studies of term placenta. However, there is increasing evidence that placental transport in early pregnancy may differ from that at term in many respects (23). An important factor that may alter the expression of particular transporter proteins is oxygen tension and blood flow to the intervillous space. Maternal blood flow to the intervillous space is established around 10 to 12 weeks of gestation (24, 25). During the first trimester, prior to the onset of maternal blood flow to the intervillous space, nutrition is histiotrophic with trophoblast phagocytosis of endometrial glandular secretions including glycogen and glycoproteins (26, 27). After 10-12 weeks gestation, maternal blood is in contact with the terminal villi of the placenta, and transfer of respiratory gases, nutrients and waste products occurs across the placental membranes. The placenta is not just a simple conduit for gases, nutrients and waste products, since it requires oxygen and nutrients for itself, and it produces metabolic products.

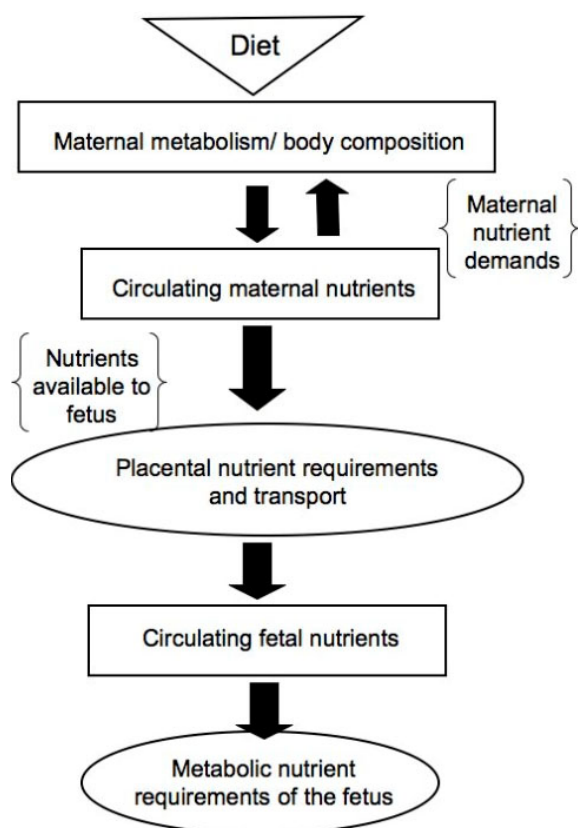


Figure 1. Overview of maternal/ fetal nutrient transport and availability.

During the last decades the picture of how nutrients enter and leave the placenta has become clearer as a result of the availability of new biochemical and physiologic techniques. In general, the placenta transfers substrates in three ways: 1. simple diffusion, 2. facilitated diffusion and 3. active transport. Simple diffusion is limited by placental blood flow and exchange area, and is the transport mechanism for oxygen, carbon dioxide and urea. The placental membranes are highly permeable to respiratory gases. Thus rapid diffusion of oxygen can readily occur from maternal to fetal blood, and of carbon dioxide from fetal to maternal blood. Because diffusion of respiratory gases occurs so readily, a rate-limiting factor for their transfer can be blood flow to and from the site of transfer. Fetal hemoglobin has a higher affinity for oxygen and a lower affinity for carbon dioxide than maternal hemoglobin. This difference in hemoglobin favors the transfer of oxygen to the fetus and carbon dioxide to the mother.

Glucose and lactate are the main substrates transported by facilitated diffusion. Facilitated transport depends on carrier proteins and moves substrates down an existing concentration gradient without energy consumption. The glucose transporter (GLUT). family uses a concentration gradient of the transferred substrate, whereas other systems are dependent on secondary substrates to drive nutrient transfer. The most common of

these substrates is sodium that moves from the higher concentration outside the cell into the cell, where the concentration is lower. Active transport, the primary transport mechanism for amino acids, also involves carrier proteins but is dependent on an energy supply.

4. CARBOHYDRATE METABOLISM IN PREGNANCY

4.1. Glucose metabolism and transport

Glucose is the main carbohydrate transported across the placenta from mother to fetus, and it is a primary source of energy for the fetus. Since gluconeogenesis is limited in the fetus, glucose must be derived from the maternal circulation (28). The primary driving force for glucose transfer across the placenta is the concentration of fetal glucose (28). Diminished fetal glucose concentrations are associated with a decrease *in utero*-placental glucose utilization and enhanced maternal-fetal glucose transfer rates. Conversely, maternal hypoglycemia is associated with lower maternal-fetal glucose transfer and fetal hypoglycemia. During early pregnancy, maternal glucose tolerance is normal or slightly improved and insulin sensitivity in peripheral tissues and hepatic glucose production is normal (29-31). Insulin responses to oral glucose are also higher in the first trimester compared to those of non-pregnant women. Longitudinal studies of glucose tolerance during pregnancy have shown a progressive increase in insulin resistance (32). Glucose clamp studies later in pregnancy have indicated that insulin sensitivity is 50-70% lower than that of non-pregnant women (29-31, 33, 34). By the third trimester, basal and 24-hour mean insulin concentrations may double (35). The exact mechanism regulating insulin sensitivity differences during pregnancy is unknown. However, it is likely influenced by hormonal changes including chorionic somatomammotropin, progesterone, cortisol, and prolactin. Inflammatory cytokines, such as tumor necrosis factor alpha (TNF alpha), also influence and disrupt insulin signaling via serine phosphorylation of insulin receptor substrate-1 (IRS1), one primary substrate of the insulin receptor (36, 37). One result of these gestational changes in insulin sensitivity is exaggerated changes in postprandial concentrations of metabolic fuels including glucose, lipid, and amino acids. Therefore, gestational insulin resistance may serve to increase nutrient availability for the fetus.

The mechanism by which glucose is transported across the placenta has been well defined. Transport of glucose across the placenta is generally via protein-mediated facilitated diffusion, carried out by a number of glucose transporters (GLUTs). Uptake of maternal glucose occurs initially across the microvillous membrane of the syncytiotrophoblast. Glucose is then transported out of the syncytiotrophoblast via the basement membrane towards the fetal capillary endothelial cells, which also have membrane-located glucose transporters. In humans, the glucose transport protein GLUT1 is found in both the microvillous and basal membranes, and appears to be the primary glucose transport protein (38). However, there are several other forms of GLUT transport proteins that are expressed in a developmental and tissue specific manner.

At term, GLUT3 is localized to the endothelial cells lining of the fetal capillaries and may be important for regulating glucose transport between these cells and fetal blood (38). GLUT4, is an insulin-responsive glucose transporter, and is present in placental stromal cells and may play a role in transporting glucose and the conversion to glycogen in these cells in response to insulin in the fetal circulation (39). GLUT8 is expressed by the placenta at term, but may be of less importance in early pregnancy (40). At term, GLUT12 is found predominantly in villous vessel smooth muscle cells and villous stromal cells (41).

4.2. Lactate

Lactate is a carbohydrate that plays a role as an additional carbon substrate other than glucose in fetal metabolism, and is supplied by the placenta to the fetus in large amounts. In contrast to postnatal life where lactate is produced only during anaerobic metabolic phases, the fetus is able to metabolize lactate aerobically with great efficiency (22). Lactate is also produced by the placenta from glucose under aerobic conditions and is transferred to the fetus via carrier-mediated mechanisms (22). Lactate is used either directly as a fuel for energy, in gluconeogenesis or as a fetal substrate reservoir.

4.3. Carbohydrate metabolism in preeclampsia

Several studies have reported that insulin resistance is more common among women with preeclampsia, as well as evident among women who later develop preeclampsia (18, 42-45). The cause of the increase in insulin resistance among women who later develop preeclampsia as well as women with the syndrome has not been fully explained. However, based on the pathophysiology of the syndrome several possibilities exist including increased inflammation, the metabolic syndrome and obesity. Studies have reported elevations in inflammatory cytokines (TNF alpha and interleukin-6), and markers (C reactive protein), during normal pregnancy and a further elevation in these markers among women with preeclampsia (46-51). Inflammation is a powerful biological mediator and has been clearly demonstrated to contribute to insulin resistance (37). The metabolic syndrome is characterized by a group of metabolic risk factors including: abdominal obesity, dyslipidemia (high triglycerides and LDL cholesterol, and low HDL cholesterol), insulin resistance, pro-thrombotic state, and pro-inflammatory state. The dominant underlying risk factors for the metabolic syndrome are obesity and insulin resistance. The incidence of obesity has increased significantly over the past several years in the United States, such that 30% of adults are obese (52). Obesity increases the risk of preeclampsia 2 to 3 fold (53). In addition, because of the absolute numbers of overweight and obese women in the United States, obesity is likely the single most significant risk factor contributing to preeclampsia and accounting for as much as 15 and 32% of the population attributable risk of preeclampsia. Since inflammation, the metabolic syndrome, insulin resistance, dyslipidemia, and a pro-thrombotic phenotype are all associated with obesity, it is likely that obesity is also contributing significantly to the presence of these conditions in preeclampsia.

While obesity and insulin resistance contribute to an increased risk of preeclampsia, these conditions may also contribute to an increase in nutrient availability for the placenta and fetus. Increased maternal insulin resistance would increase glucose availability as well as free fatty acids and triglycerides. These changes in nutrient availability may benefit fetal growth despite deficiencies in trophoblast invasion and placentation. While there is inconsistency in the literature between circulating glucose concentrations and fetal growth, insulin resistance is clearly associated with an increased risk of macrosomia (54, 55). In addition, positive correlations between maternal basal plasma free fatty acids and triglycerides and birth weight have also been reported (56), suggesting that lipid flux across the feto-placental unit may contribute to macrosomia. It is also interesting that infants of women with preeclampsia or pregnancy induced hypertension (PIH), that are also born pre-term have better postnatal outcomes compared to similarly pre-term infants born to women without preeclampsia or PIH (57). These results support the hypothesis that the metabolic alterations associated with preeclampsia may benefit fetal growth and/or development despite a less than optimal intrauterine environment.

Few studies have been published investigating differences in GLUT transporters in the placentas of women with preeclampsia compared to women with uncomplicated pregnancy outcomes. Interestingly, a recent study by Zamudio *et al.* found that immunoreactive GLUT1 is significantly decreased in the basal membranes of placentas of women at higher altitude compared to placentas from women at low altitude, and thereby suggests that hypoxia not only affects fetal growth by limiting oxygen but may also negatively influence placental glucose transport (58). However, differences in the amount of immunoreactive GLUT1 in placentas from women with preeclampsia have not been reported yet.

5. LIPID METABOLISM IN PREGNANCY

The diverse effects of pregnancy include a profound impact on lipid metabolism. Several comprehensive reviews describe the changes in lipid metabolism that occur during normal pregnancy and their importance for fetal development (59, 60). This section summarizes some of these changes and provides a reference for discussion of differences in lipid metabolism in preeclampsia.

Changes in lipid metabolism promote the accumulation of maternal fat stores in early and mid pregnancy (61). In contrast, this pattern shifts to a catabolic state of net breakdown/mobilization of adipose lipid depots during the second half of pregnancy (62, 63). 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. One striking example of this mobilization of lipid depots is the increase in free (non-esterified), fatty acid (FFA), concentrations in maternal plasma with advancing gestation. Essential fatty acids and long chain polyunsaturated fatty acids are important for

fetal development and growth. At 12-14 weeks of normal pregnancy, insulin sensitivity is slightly increased, but then decreased during the rest of pregnancy (29, 64). This decline in insulin sensitivity peaks during the last third of pregnancy, and is a physiological adaptation of pregnancy that helps ensure availability of glucose and FFA for the fetus.

Circulating concentrations of FFAs are regulated in part by hormone-sensitive lipase in maternal adipocytes. One action of insulin is to inhibit this enzyme, decreasing adipocyte triglyceride hydrolysis and limiting serum FFA and glycerol concentrations. Gestational insulin resistance, therefore is likely in part responsible for increased release of FFA and glycerol from adipocytes (63). In addition, the high levels of plasma FFA typically observed during last half of pregnancy may actually contribute to some of the gestational insulin resistance (65). The inflammatory cytokine TNF alpha and the adipokine leptin may also play a role in gestational insulin resistance (64, 66). The lipolytic action of human placental lactogen (hPL), which reaches very high levels during late gestation, also appears to contribute to the increase in FFA (67).

Much of the glycerol and FFA released from adipocytes are taken up by the liver and re-esterified for synthesis of very low-density lipoprotein (VLDL) triglycerides. Higher estrogen concentrations and decreased hepatocyte beta-oxidation also lead to increased hepatocyte VLDL production. By term, plasma triglycerides increase by 50-300% over non-pregnant levels at which time higher amounts of triglycerides are found not only in VLDL but also in intermediate density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) (59, 68-70). Lipoprotein lipase, tethered to the luminal side of capillaries and arteries of extra-hepatic tissues, hydrolyzes lipoprotein triglycerides to produce FFA and monoacylglycerol. These lipolysis products are predominantly taken up locally to meet the needs of that tissue. This activity promotes triglyceride clearance from the circulation. However, adipose tissue lipoprotein lipase activity decreases substantially during the last third of pregnancy as a result of insulin resistance and other hormonal influences. The result is a decrease in the rate of removal of triglyceride-rich lipoproteins from the circulation (63). Therefore, increased lipid production and decreased lipid removal likely contribute to the dramatic increase in postprandial and fasting triglycerides evident by late gestation (63).

Despite the enhanced transfer of lipolytic products from adipose tissue into the maternal circulation, their placental transfer is relatively low (71). During early gestation, embryonic and fetal lipids are derived from maternal free fatty acids and glycerol crossing the placenta, whereas in advanced gestation there is a gradual shift to de novo synthesis in fetal tissues (72). Ketogenesis is not active in the fetus, however ketones are easily transferred by simple diffusion through the placenta into the fetal plasma and reach the same level as in the mother (71, 73, 74). For example, fasting during pregnancy is associated with maternal lipid oxidation and an increase in ketones

such as beta-hydroxybutyrate (75, 76). The fetus benefits from this product of maternal fatty acid metabolism since ketone bodies can be used not only as fuels (77), but also as lipogenic substrates (73, 78). Enhanced lipolysis and ketogenesis allows pregnant women to use stored lipid for energy and limits protein catabolism.

In contrast to ketones, maternal triglycerides do not directly cross the placenta (71, 79, 80). However, triglyceride rich lipoprotein particles are important in the transfer of essential fatty acids to the fetus. An elaborate placental transport process ensures that adequate amounts of fatty acids, originally packaged in maternal lipoprotein triglycerides, are delivered to the fetus. Components of this transport process include LDL and VLDL/apo E receptors in the placenta, placental lipoprotein lipase (not suppressed during pregnancy), placental phospholipase A2, and intracellular placental lipases (60, 81-83). Lipoprotein lipase, present only on the maternal surface of the placenta, makes FFA available by hydrolyzing triglycerides carried by maternal VLDL (80). Both free fatty acids and glycerol (but not triglycerides) can readily cross the membranes of the placental syncytiotrophoblast. Glycerol and free fatty acids can also cross the placenta via the action of membrane-bound and cytosolic fatty acid binding proteins (84). These proteins are important in determining the direction and amount of net flux of fatty acids. After uptake by trophoblast cells, fatty acids are re-esterified to provide a fat reservoir. After intracellular hydrolysis releases fatty acids to fetal plasma, they bind α -fetoprotein and are transported to the fetal liver (60). However, free fatty acids are mainly incorporated into lipids and are therefore not a major energy source for the fetus. A direct relationship between maternal triglycerides and birth weight has been found in humans. Severe correction of maternal hypertriglyceridemia (as with hypolipidemic drugs) has negative effects on fetal growth and development (60).

The placenta delivers as much as 50% of the total daily fatty acid requirement of the fetus, all of the essential fatty acids, the fat soluble vitamins, and cholesterol-derived precursors of steroid hormones to the fetus. Intrauterine requirements of essential fatty acids in the human fetus during the last trimester of fetal development have been estimated to be around 400 mg/kg/day (72). In tissues such as the brain, where lipid makes up nearly 50% of the dry weight, around half the total lipid content is composed of long chain polyunsaturated fatty acids (LCPUFAs) (85), arachidonic acid (20:4,n-6) and docosahexaenoic acid (22:6,n-3) are considered the most important LCPUFAs. Polyunsaturated fatty acids of the n-6 and n-3 families are essential dietary fatty acids. It is known that in the systemic circulation, PUFA levels are mainly derived from dietary intake. PUFA distribution and storage is organ and tissue specific. Selective transportation of PUFAs from the maternal to the fetal circulation has been reported to be in the order of docosahexaenoic acid (22:6,n-3) > linolenic acid (18:3) > linoleic acid (18:2) > oleic acid (18:0) > arachidonic acid (20:4,n-6) (86). The n-6 polyunsaturated fatty acids are involved in inflammatory reactions, whereas n-3 polyunsaturated fatty acids are reported to protect against inflammation (87).

Maternal cholesterol levels increase during pregnancy, with a 50-60% rise over non-pregnant levels by term (88). Cholesterol is used by the placenta for steroid synthesis and fatty acids are used for oxidation and membrane formation. Changes in maternal total cholesterol concentrations reflect changes in the various lipoprotein fractions. Although the placenta can synthesize cholesterol, under normal circumstances cholesterol is derived from maternal blood via the interaction of circulating LDL particles with LDL receptors on the microvillous membrane of the syncytiotrophoblast, followed by internalization of LDL particles by receptor-mediated endocytosis. HDL cholesterol increases by 12 weeks of gestation in response to estrogen and remains elevated throughout pregnancy (89). Total and LDL cholesterol concentrations increase in the second and third trimesters. VLDL and triglycerides initially decrease in early pregnancy, but then increase until term. In the second half of pregnancy, lipoprotein particle clearance is altered as result of decreased lipoprotein lipase (LPL) activity in adipose tissue and the liver, and because of increased LPL activity in the placenta (90). Reversal of the "physiologic hyperlipidemia" of pregnancy begins within hours of delivery and is essentially complete by 6 to 10 weeks postpartum (68).

5.1. Dyslipidemia of preeclampsia

Marked dyslipidemia occurs with preeclampsia (42, 70, 88, 91). In many ways this dyslipidemia represents an accentuation of the lipid changes noted in normal pregnancy. Mean plasma triglyceride and FFA concentrations increase about 2-fold on average in women with preeclampsia relative to women with uncomplicated pregnancy (92-94). About one third of women with preeclampsia evidence plasma triglyceride concentrations above 400mg/dL (94), greater than the 90th percentile measured in randomly selected women at 36 weeks gestation (59). This difference reflects a marked increase in the concentration of triglyceride-rich lipoproteins (especially VLDL) (95). The hypertriglyceridemia of preeclampsia is accompanied by a decrease in cardioprotective HDL cholesterol relative to normal pregnancy (95, 96). However, not all women with preeclampsia develop gestational dyslipidemia and some women with profound dyslipidemia have an uncomplicated pregnancy outcome. This pattern fits with the concept that the preeclampsia syndrome is multifactorial and heterogeneous (97).

Dyslipidemia is evident during the first and second trimester, far preceding the clinical manifestations of preeclampsia (93, 98-101). HDL-cholesterol is reduced at earliest measurement (20 weeks gestation), and then throughout gestation in women who later develop the syndrome, again implicating dyslipidemia in the pathophysiology (101). Lower HDL may result from higher triglycerides since the two are metabolically linked (102, 103). Higher mean concentrations of the major FFAs (oleic, linoleic, palmitic), are detectable by 16 to 20 weeks of gestation in women who later develop preeclampsia (93, 98). Abnormal elevations in fasting triglycerides are reported to occur as early as 10 weeks of gestation in

women who later develop preeclampsia (100). Interestingly, early hypertriglyceridemia is associated with increased risk of early onset preeclampsia (preeclampsia developing before 36 weeks of gestation), but not late onset preeclampsia (104). This adds to evidence that early- and late-onset variants of the syndrome are pathogenically distinguishable and is consistent with the notion of multiple pathways to preeclampsia.

Relative to normal pregnancy, total cholesterol and LDL cholesterol levels are generally not altered during preeclampsia (105). According to two reports, however, women with high total cholesterol during the first trimester are at increased risk of preeclampsia (106, 107). This is interesting given data that cholesterol is also increased months postpartum in many women with a history of preeclampsia, possibly suggesting a disorder in cholesterol metabolism in these women even though this may be masked during late pregnancy (108).

Maternal plasma levels of nonesterified polyunsaturated fatty acids are reported to be lower in women with preeclampsia as compared to women with uncomplicated pregnancies. This was evident for maternal plasma levels of linoleic acid (18:2), linolenic acid (18:3), and eicosapentaenoic (20:5), while arachidonic acid (20:4,n-6), and docosahexaenoic acid (22:6,n-3), levels were not changed in preeclampsia compared to those in control pregnancies (109). In placental tissues total concentrations of nonesterified polyunsaturated fatty acids were found to be lower in preeclamptic pregnancies compared to tissue from control pregnancies. However the PUFA pattern in the placental tissue was different from the pattern in the maternal circulation with lower n-6 and n-3 polyunsaturated fatty acids but not altered linoleic and linolenic acid concentrations (110). These data suggest that the lower placental tissue levels of PUFAs may be related to metabolism and not dietary intake, leading to the speculation that placental oxidative stress and increased conversion of arachidonic acid (20:4,n-6), to thromboxane may contribute to the lower concentrations of polyunsaturated fatty acids in preeclampsia.

The finding of early lipid changes fits with the notion that dyslipidemia promotes dysfunction of the maternal vascular endothelium. The early lipid changes also beg the question of whether lipid abnormalities are present before pregnancy in women who later develop preeclampsia, and this condition is perhaps unmasked or amplified by the physiologic changes of pregnancy. While dyslipidemia may contribute to the pathophysiology of preeclampsia, therapeutic intervention is unwise. Considering the direct relationship between maternal triglyceride concentration and newborn weight, the potential for adverse effects of lipid lowering agents on fetal health must be kept in mind. It is biologically plausible that exaggerated hyperlipidemia occurs as a response to signals (leptin, human placental lactogen, etc.), from the feto-placental unit to mobilize more substrate for the poorly perfused placenta and fetus. Although intrauterine fetal growth restriction (IUGR), is a common complication of preeclampsia, many babies born to women

with preeclampsia are not small for gestational age (111). Pregnancies complicated by IUGR without preeclampsia have placental lesions similar to preeclampsia but without a maternal syndrome (no hypertension or proteinuria). Women with IUGR infants without the maternal syndrome do not develop hypertriglyceridemia (112). Furthermore, as a group these women actually have lower VLDL₂, IDL, and cholesterol concentrations compared to women with uncomplicated pregnancies (112). One hypothesis may be that failure to mobilize/synthesize lipids in the face of inadequate placental perfusion contributes to fetal growth restriction. In addition, dyslipidemia may increase lipid availability for fetal/placental development but also contribute to maternal vascular dysfunction, such as the case in preeclampsia.

6. AMINO ACID METABOLISM AND TRANSPORT IN PREGNANCY

Lower circulating concentrations of maternal amino acids during pregnancy have been noted for many years (113-115). The concentration of most amino acids in the maternal circulation decrease early in pregnancy, remain lower throughout pregnancy and increase to non-pregnant levels after delivery (115, 116). The mechanism responsible for this change in maternal plasma amino acids during pregnancy is likely related to changes in renal function since amino acids are readily filtered by the glomerulus and amino acid reabsorption by the proximal tubules is decreased during pregnancy (116-119). In addition, these changes in circulating amino acid concentrations are likely affected by changes in metabolism, specifically increases in protein synthesis needs (120). Conversely, these changes are unlikely to be the result of changes in plasma volume (121-123). During pregnancy the increased demand for energy and protein for fetal and placental growth are not met by dietary protein. Paradoxically, there is evidence that increases in maternal protein intake are associated with smaller babies and poorer pregnancy outcomes (124). Instead amino acid and protein requirements are satisfied by metabolic changes that are determined by hormonal signals, maternal body composition and the mobilization of nutrient reserves (125).

Amino acids comprise an important fetal nutrient. Amino acids are not only required by the fetus for protein synthesis, but they are also metabolized by the fetus. Amino acids have been estimated to comprise as much as 20 to 40% of the energy required by the fetal-placental unit (126, 127). The total protein gain during pregnancy is estimated to be about 925 grams (128). The fetus contributes the most to this net protein gain. Longitudinal analysis of nitrogen balance before and during pregnancy indicates that nitrogen retention is 0.2grams/day before pregnancy and -0.4, 0.5 and 1.2 grams/day at 12, 23 and 34 weeks gestation respectively (129). Since the nutrient content of maternal blood does not simply reflect dietary intake and protein intake does not change substantially during pregnancy, there must be adaptations that alter protein and nitrogen metabolism during pregnancy. Protein turnover represents the continual movement of amino acids

into and out of protein (130, 131). As such protein turnover is estimated to be 250 grams of protein each day for adult women compared to the 50 to 70 grams of protein obtained by the diet. In general, protein turnover is reported to increase in normal pregnant women by 15% in the second trimester and by 25% in the third trimester compared to non-pregnant women (120, 132-136). In addition, higher protein turnover in normal pregnant women in the second trimester has been estimated to account for 26% of the variation in infant birth length adjusted for infant sex and gestational age, and independent of maternal height, lean body mass and protein intake (120). Amino acids are either used in the synthesis of protein or are oxidized. Urea is formed from the release of the amino groups from amino acids as they are oxidized for energy. A recent study by Duggleby reported that the absolute difference in maternal amino acid oxidation was widely variable in normal pregnant women between 17-19 and 26-29 weeks gestation (128). However, the change in maternal amino acid oxidation between mid and late pregnancy was inversely related with infant growth, such that the change in maternal amino acid oxidation accounted for 34% of the variation in birth weight (128). This is a surprisingly strong relationship given that previous reports of insulin sensitivity have been reported to account for as much as 28% of infant birth weight (137). These data support the role of amino acids as an important fetal nutrient, and maternal metabolic changes that spare amino acids for fetal and placental use support growth.

There are over twenty different amino acids found in plasma, both "essential" (i.e. not some synthesized by human tissues). and "nonessential". Transport of amino acids to the fetus during pregnancy occurs via the microvillous and basal membranes of the syncytiotrophoblast. Plasma concentrations of most amino acids are higher in the fetus compared to the mother, and higher in the placenta compared to the fetus, indicating an active transport of amino acids by the placenta (138-140). Generally, amino acids are transported to the fetus and undergo metabolism through one of three main routes: 1. utilization for carbon and nitrogen accretion in the growing fetus, 2. utilization for interconversion to other substrates, which then may be used for carbon and nitrogen accretion, or 3. amino acids serve as oxidative fuels for the placenta or fetus, resulting in the production of carbon dioxide, water and ammonia. The transport of amino acids across the trophoblast involves three fundamental steps: 1. uptake of amino acids from the maternal circulation across the microvillous membrane, 2. transport of amino acids through the trophoblast cytoplasm and 3. transport of amino acids out of the trophoblast across the basolateral membrane into the fetal circulation. As a result of pioneering work, in particular originating from Christensen *et al.* a great variety of mammalian amino acid transport proteins have been identified, most of them are distributed within both the placental microvillous and the basolateral membranes. Historically, placental amino acid transport systems have been arranged based upon whether they were sodium-dependent or sodium-independent, and whether systems preferred cationic, zwitterionic or anionic substrates (141-144). System A, Beta and Gly are

associated with sodium-dependent accumulation of small neutral amino acids, beta amino acids (i.e. taurine), and glycine respectively (145-148). For most neutral amino acids, sodium-dependent transporter systems such as system A and Beta are present in the microvillous membrane and the driving force for the accumulation of these amino acids is the sodium gradient across the microvillous membrane, which is dependent on the activity of sodium transporters such as Na⁺/K⁺ ATPase. For most amino acids there is a net transfer from the maternal to the fetal circulation, except for aspartate and glutamate. For some amino acids, it has been shown that their delivery to the fetus is not solely determined by transplacental transport, but also by their production and/or utilization within the placenta (140). In addition, studies have demonstrated that amino acid delivery to the fetus can be enhanced by increasing their concentration in the maternal circulation (149-151). Please refer to the excellent recent review by Jansson for a more detailed review of placental amino acid transport systems (145).

6.1. Amino acids in preeclampsia

In general, there have been relatively few studies investigating amino acids in preeclampsia. Most studies that have investigated differences in amino acids in preeclampsia have focused on single amino acids, primarily L-arginine, homocysteine and asymmetric dimethylarginine (ADMA), because of their potential to influence maternal vascular function via alterations in nitric oxide synthase activity (44, 121, 152-158). Most of these studies have reported finding higher maternal concentrations of homocysteine and ADMA and lower concentrations of L-arginine. In some cases these differences have been associated with differences in maternal vascular function, markers of vascular dysfunction or insulin resistance (44, 121, 155).

In contrast to studies of single amino acids, there have been few studies that have investigated amino acid metabolism, placental transport or differences in maternal and fetal amino acids in preeclampsia. Three studies have reported finding higher maternal amino acid concentrations in preeclampsia compared to normal pregnant women (159-161); and one small study has reported no difference in maternal amino acid concentrations in preeclampsia (162). In contrast, D'Aniello *et al.* reported an approximate five-fold lower L-arginine concentration in the blood of women affected by preeclampsia compared to control pregnant women, and lower amino acid concentrations overall, but to a lesser extent than that of L-arginine (158). In addition, a study by Evans *et al.* reported finding higher amino acid concentrations in the cord blood of infants of women with preeclampsia compared to women with uncomplicated pregnancies. This increase in cord blood amino acid concentrations was present in both appropriately grown infants and small for gestational age infants (161). These data indicate that, in contrast to IUGR, preeclampsia may be associated with enhanced placental amino acid transport or reduced fetal amino acid utilization (161).

Placental transport of amino acids is diminished in pregnancies with intrauterine growth-restricted (IUGR).

infants, contributing to the decrease in cord blood amino acid concentrations and reduced growth (163-166). In contrast, approximately a third of infants of women with preeclampsia are small for gestational age (SGA), or evidence growth restriction. However, only a few studies have investigated placental amino acid transport in preeclampsia. A study by Dicke *et al.* investigated the uptake of alpha-aminoisobutyric acid (System A), by microvillous vesicles between normal pregnancies, and those complicated by pregnancy-induced hypertension, non-insulin dependent diabetes mellitus and SGA (167). There was no difference in amino acid uptake in the samples from women with pregnancy-induced hypertension compared to controls, but a decrease in uptake in pregnancies with SGA infants. Similarly, a recent study has also reported finding no difference in System A amino acid transport activity in placentas from women with preeclampsia with and without SGA infants, but lower transport activity in placentas from women without preeclampsia and with SGA infants compared to placentas from women with uncomplicated pregnancies (168). A study by Speake *et al.* reported an increase in the placental basal membrane transport of L-arginine in preeclampsia compared to women with normal pregnancies (169). Malina *et al.* noted no difference in the expression of mRNA for System A transporters in placentas from women with preeclampsia compared to normal pregnant women (170).

7. SUMMARY AND PERSPECTIVES

Pregnancy is a remarkably dynamic metabolic state, and much has been learned in the past few decades about maternal-fetal-placental metabolic interactions. There are striking changes in insulin sensitivity, lipid metabolism and mobilization, and in amino acid concentrations, transport and oxidation during pregnancy. In many cases, these changes have been associated with differences in fetal growth. Interestingly, the pregnancy syndrome preeclampsia demonstrates exaggerations of these metabolic changes notably: increased insulin resistance, dyslipidemia and elevations in circulating maternal and fetal amino acids. These metabolic differences, insulin resistance and dyslipidemia, may contribute in part to the pathophysiology of the syndrome given that they precede the clinical manifestations of the syndrome and are capable of affecting maternal vascular function. In addition, the role and influence of insulin resistance and dyslipidemia in metabolism and fetal growth in pregnancy and preeclampsia has received significant attention. Furthermore, while the role of amino acid metabolism and transport in fetal growth and IUGR has been investigated for many years, far less attention has been given to the role and importance of amino acid metabolism and transport in preeclampsia. However, based on recent data demonstrating the importance of maternal amino acid oxidation and placental amino acid transport on fetal growth, and differences in maternal and fetal amino acid concentrations in preeclampsia compared to uncomplicated pregnancies and IUGR, this is an area that is likely to receive increased attention in preeclampsia research.

8. ACKNOWLEDGEMENTS

This work was supported in part by National Institutes of Health grant number P01-HD30367

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Key Words: Pregnancy, Preeclampsia, Carbohydrate, Lipid, Amino Acid, Metabolism, Transport, Placenta, Review

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