Section 1 Chapter 1

Nutritional regulation and requirements for pregnancy and fetal growth

Maternal adaptations to pregnancy and the role of the placenta

Leslie Myatt and Theresa Powell

Delivery of an optimally grown, viable infant defines a successful pregnancy. Optimal growth is achieved by the interaction of maternal, placental, and fetal systems to deliver maternal nutrients to the placenta, transfer them to the fetus, and maximize their utilization for fetal growth. Pregnancy is characterized by profound changes in the maternal immune, metabolic, cardiovascular, and renal systems to ensure a successful pregnancy and adequate fetal growth. The fetal-placental unit secretes many hormonal signals, the roles of which include redirecting maternal physiology and metabolism to direct substrate toward the fetus and support normal fetal growth. The physiological adaptations of pregnancy begin shortly after conception, indeed before the establishment of a fetal-placental unit, and thus in their early phases must be directed by maternal signals, including those from the corpus luteum. Subsequently feto-placental signals play a major role in regulation of maternal metabolism. This chapter describes the maternal adaptation to pregnancy and the role of the placenta in nutrient transfer to the fetus.

Adaptive changes in maternal physiology

Cardiovascular system

The changes in the cardiovascular system seen in pregnancy are by far the largest physiological challenge this system will face throughout the life cycle and include anatomical changes, increased blood volume and cardiac output, and a decrease in systemic vascular resistance. Ventricular wall muscle mass increases in the first trimester [1], followed by an increase in end-diastolic volume in the second and early third trimesters to increase cardiac compliance. Collagen softening is seen, resulting in increased compliance of capacitive and conductive vessels; this change occurs within 5 weeks of conception [2]. Blood volume increases from 6 to 8 weeks gestation onward by 45% to reach approximately 5 l at 32 weeks gestation [3]. This increase is greater with multifetal gestation and correlates with fetal weight. The mechanism is unknown but occurs in the absence of a fetus and may be related to the renin-angiotensin system or relaxin. Red blood cell mass also increases by 20% to 30% in pregnancy, reflecting increased production of red blood cells, but the net result is physiological hemodilution, potentially a protective effect because it reduces blood viscosity to counter the predisposition for thromboembolic events in pregnancy [4] and may also be beneficial for placental perfusion.

Cardiac output (heart rate $\times$ stroke volume) increases by 30% to 50% in pregnancy [5] because of increases in both stroke volume and heart rate. The early increase is due to the rise in stroke volume [5], reflecting the increase in ventricular mass and end-diastolic volume. Stroke volume declines toward term, but heart rate increases from 5 to 32 weeks gestation by 15 to 20 beats per min and is maintained thereafter to maintain cardiac output. Blood flow to the uterus increases 10-fold (from 2% to 17% of cardiac output) in gestation, reaching 500 to 800 ml/min at term. Arterial blood pressure and systemic vascular resistance decrease from as early as 5 weeks gestation and reach a nadir in the second trimester, after which blood pressure increases again. This is thought to be hormonally regulated, perhaps by progesterone, the endothelial-derived vasodilator nitric oxide, or prostaglandins, but also potentially by the introduction of the low-resistance uteroplacental circulation [6]. The decrease in systemic vascular resistance may be the stimulus to increase heart rate, stroke volume, and cardiac output in early gestation. Maternal tidal volume increases by 40% in pregnancy, resulting in hyperventilation and a decrease in partial pressure of carbon dioxide in blood.

Renal system

Renal size, weight, and volume increase in gestation because of increases in renal vascular and interstitial volume [7] together with a marked increase in dilation of the collecting system. Renal blood flow increases 60% to 80% by mid-gestation and is 50% greater at term [8]. Glomerular filtration rate increases up to 50% at the end of the first trimester, with a modest increase in creatinine clearance. These changes are initiated in the luteal phase of the menstrual cycle [9]. In the rat, there is strong evidence that the ovarian hormone relaxin is responsible for renal hemodynamic and osmoregulatory changes in pregnancy [10]. Similarly, in humans, relaxin appears to play a role in establishing the renal response [11]. However in the absence of relaxin, as in patients with ovum donation and no corpus luteum, a renal response, although subdued, is still seen, suggesting that some other mechanism may also operate. In the luteal phase of the cycle, luteinizing hormone stimulates relaxin secretion from the corpus luteum, and this response is augmented and maintained by human chorionic gonadotropin (hCG) after conception.

The endocrinology of pregnancy

The concept of the feto-placental unit originated in the 1950s but it is now recognized that the placenta and in particular the syncytiotrophoblast is a powerful endocrine organ that synthesizes many steroid and peptide hormones whose role is to ensure fetal survival and growth by directing maternal metabolism and fetal growth and development. Human chorionic gonadotropin (hCG) is the earliest biochemical marker of pregnancy produced by the embryo (7–8 days after fertilization) and with a doubling time of 31 hours after implantation [12]. The major biological role of hCG in early pregnancy is to rescue the corpus luteum from demise and maintain progesterone (and presumably relaxin) production until the luteal-placental shift in progesterone production at 9 weeks gestation. Following this time, the placenta is the major source of progesterone synthesis from maternal cholesterol, reaching 250 mg/day at term from 25 mg/day in the luteal phase. The major roles of progesterone in pregnancy may be in dampening immune responses and maintaining smooth muscle quiescence. Indeed, in animal species, high circulating progesterone is associated with myometrial quiescence and delayed onset of labor [13]. Similarly progesterone may have major nongenomic relaxatory effects on the vasculature [14].

The placenta is also the major site for estrogen synthesis. The predominant estrogen in pregnancy is estriol, formed as a result of interaction of fetal and placental tissues through which fetal adrenal dehydroepiandrosterone sulfate (DHEAS) is converted to estrogens by placental sulfatase and aromatase. Placental estrogen production increases throughout gestation. Estrogen has been shown to have a powerful effect in increasing uterine blood flow and may therefore facilitate fetal nutrition by increasing placental oxygenation and nutrient delivery. It also prepares the breast for lactation, affects the renin-angiotensin system, and stimulates production of hormone-binding globulins in the liver.

Maternal metabolic changes in gestation

During pregnancy, an adaptation of maternal metabolism functions to ensure normal fetal growth throughout gestation and neonatal growth during lactation. Thus, there is a period of adipose tissue accretion in early gestation followed by insulin resistance to increase glucose availability for the fetus and lipolysis to increase fatty acid availability. The maternal metabolic reprogramming is believed to be directed by placental hormones. Insulin secretion increases during early pregnancy and more than doubles, resulting in a 30% higher mean insulin level by the third trimester. Skeletal muscle, which is the major site of glucose disposal, and adipose tissue both become highly insulin resistant during the second half of pregnancy. There is a 50% reduction in insulin-mediated glucose disposal, requiring an increase in insulin secretion to maintain euglycemia [16]. Failure of the mother to increase insulin will lead to maternal hyperglycemia and thus fetal hyperglycemia with consequent fetal hyperinsulinemia, macrosomia, and fetal hypoxia. Insulin also loses its ability to suppress whole-body lipolysis, leading to increased postprandial free fatty acid levels and a decline in maternal adipose tissue [17]. Total plasma lipids, triglycerides, free fatty acids, and cholesterol increase after 24 weeks gestation [18] with increases in pre-B lipoprotein, high-density lipoprotein (HDL) cholesterol in early pregnancy, and low-density lipoprotein (LDL) cholesterol in late pregnancy. The action of insulin is mediated through insulin receptors that are

regulated by phosphorylation. The degree of glucose uptake and insulin resistance is also regulated by the level of insulin receptor substrate-1 (IRS-1) protein and levels of the p85α subunit of phosphoinositide 3-kinase, which docks to IRS-1 (reviewed by Barbour et al. [19]).

Early pregnancy as a determinant of placental and fetal growth

Maternal nutrition around the time of conception may have important effects on gestational length, fetal growth trajectory, and postnatal growth and health (for review, see Cross and Mickelson [20]. Specific nutrients and general nutritional status of the mother may play key roles in altering the development of the placenta, effects that have direct consequences on the fetus [21]. Blastocyst development and subsequent implantation potential are reduced in diabetic mothers and when culturing embryos in high D-glucose [22]. Both essential and nonessential amino acids affect mouse blastocyst development during in vitro culture by enhancing postimplantation development and increasing implantation potential [23]. The mammalian target of rapamycin (mTOR) signaling pathway mediates the effects of amino acids in stimulating blastocyst growth and invasion. Adequacy of amino acids is detected by the mTOR system, and invasive capacity is upregulated if nutrients are available. Insufficient nutrients result in a lack of invasiveness, and the implantation window may be lost [24]. Ghrelin, a hormone known to stimulate appetite, may also affect early development. Treatment with ghrelin reduces the number of inner cell mass and trophectoderm cells in blastocysts, similar to the effect of a low protein diet [25].

Once implantation is successful and the pregnancy is established, there is little variation in the size of the human fetus up to 16 weeks gestation, and the early conceptus has low absolute energetic and anabolic needs. Excluding chromosomal and genetic disorders, the dominant determinant of variation in fetal size is supply of nutrients and oxygen. Early fetal nutrition may be provided by endometrial glands that remain functional until at least 10 weeks gestation. These glands have intact pathways to the intervillous space and secrete carbohydrates and lipids as well as growth factors, which provide a source of histotrophic nutrients and direct the differentiation of the developing villous tissue (for review, see Burton et al. [26]).

The effect of maternal nutrient availability

In light of the low total nutrient requirements in early pregnancy, data are rapidly accumulating implicating early gestation as a pivotal period for determining placental and fetal growth trajectories. Maternal nutrient availability and metabolic status may not be fully equivalent as determinants of fetal growth, as is apparent in the analysis of exposure to food shortage during different periods of gestation for individuals born around the time of the Dutch famine. In pregnancies affected by famine primarily during early gestation, offspring were of normal size at birth and showed increased risk for cardiovascular disease later in life [27]. The early pregnancy effect may be related to insufficient fat deposition in the mother during this critical period of pregnancy [28]. Likewise, hyperemesis in the first half of pregnancy, which could be considered a form of maternal undernutrition in early pregnancy, generally results in only small reductions in birth weight [29]. In pregnancies in which the Dutch famine was experienced later in pregnancy, growth restriction as well as increased risk for metabolic diseases in adulthood resulted [30].

In animal models in which nutrient restriction can be manipulated to distinct periods of gestation, differential long-term effects on the offspring have been documented. In pregnant sheep, early maternal nutrient restriction appears to have effects primarily on the brain (smaller brain and impaired cognitive function), whereas maternal nutrient restriction later in pregnancy results in small fetuses that have an increased risk of developing glucose intolerance, insulin resistance, and increased fat mass (for review, see Symonds et al. [31]). These data suggest that nutrient availability alone is not the primary factor regulating fetal and placental growth rates or birth weight. In fact, several observational studies suggest that only in quite severe maternal malnutrition is birth size affected. The balance of macronutrients in the diet of pregnant women has been suggested to play a role in determining birth weight, with dietary protein in early pregnancy likely to be an important factor [32]. The metabolic status of the mother – that is, insulin sensitivity, glycemic control, and inflammatory status during the early pregnancy window – may have profound effects on the fetus in utero and later in life. The relationship between maternal nutritional availability and the mother's ability to maintain a healthy metabolic environment for

her fetus may depend on her nutritional status before pregnancy [33] or her ability to mobilize stores during pregnancy. The interaction between maternal nutrition and metabolic status in pregnancy requires additional study.

Mechanisms linking maternal nutrition and fetal growth

The genetic contribution to fetal size at birth is primarily of maternal origin and may relate to maternal size – in particular, maternal height. Although overall genetic contributions to birth weight are low, the non-genetic maternal environmental and phenotypic influences are more important. Generally speaking, maternal nutrition may contribute to fetal growth regulation through several mechanisms.

Insulin-like growth factor 1 (IGF-1) is the primary fetal growth–stimulating factor in response to altered nutrient supply during late gestation and is under the control of fetal insulin [34]. Maternal undernutrition is associated with reduced fetal IGF-1 levels and reduced fetal growth [35].

Repeat exposure to maternal glucocorticoid leads to growth restriction. The fetus is normally protected by the action of the placental enzyme 11-βHSD. This enzyme is downregulated in periods of maternal undernutrition, which exposes the fetus to maternal glucocorticoids [36].

Maternal glycemic control in early pregnancy has been shown in both animal models and humans to be a major factor in predicting fetal growth. In humans, first-trimester maternal glycosylated hemoglobin ($Hb1_{AC}$) is the best predictor of macrosomia in pregnancies complicated by Type I diabetes [37], suggesting that growth trajectories are established early in pregnancy and are responsive to maternal metabolic signaling. Similarly, in pregnant rats, episodic hyperglycemia in early but not late pregnancy resulted in placental and fetal overgrowth [38].

Insulin and leptin are maternal metabolic indicators that may be involved in fetal intrauterine growth adaptation and long-term health. Decreases in leptin and insulin during periods of maternal nutrient restriction or high levels of these hormones in pregnant obese women may provide a signaling pathway for altering fetal growth in utero [39]. Both of these hormones have been shown to regulate placental nutrient transport functions, providing a direct link between maternal nutritional status and nutrient delivery to the fetus.

Nutritionally mediated alterations in epigenetic regulation during gestation may lead to alterations in placental function. Changes in maternal nutrition can affect the degree of DNA methylation – for example, through altered availability of methyl donors (folate) in the diet. This provides an inheritable alteration in gene expression without a change in the DNA sequence and may be important in modifying fetal and placental growth in utero and in developmental origins of adult disease [40].

Maternal nutrition also affects both placental and fetal vascular development. In pregnant rats, global undernutrition of the dam leads to intrauterine growth restriction (IUGR) and whereas the placental villous surface area increases to compensate for insufficient nutrient delivery from the mother, the extent of fetal vasculature does not [41]. In experimental iron restriction in rodents, the villous surface area is also increased, but fetal vasculature is not [42]. In sheep models of nutrition in pregnancy, both increased and decreased overall caloric intake leads to IUGR and fewer, smaller, less vascularized cotyledons [43]. The developmental signaling systems that lead to changes in placental vascular and fetal growth are not yet clearly defined and are likely to be different for early and late gestation. The interaction between developmental signaling systems and nutrient availability is an area that requires investigative attention to define more accurately the exact nature of maternal nutrient requirements in early pregnancy.

The role of the placenta in regulation of maternal metabolism and fetal growth

Secretion of human chorionic somatomammotropin and growth hormone

Human chorionic somatomammotropin (hCS; also called human placental lactogen, hPL) has structural and biological similarities to human growth hormone (hGH) and prolactin. hCS is produced only by syncytiotrophoblast, but production increases 30-fold in gestation, reaching 1 to 4 g/day at term. However the role of hCS is still not fully elucidated. It is suggested to control maternal metabolism, resulting in reductions

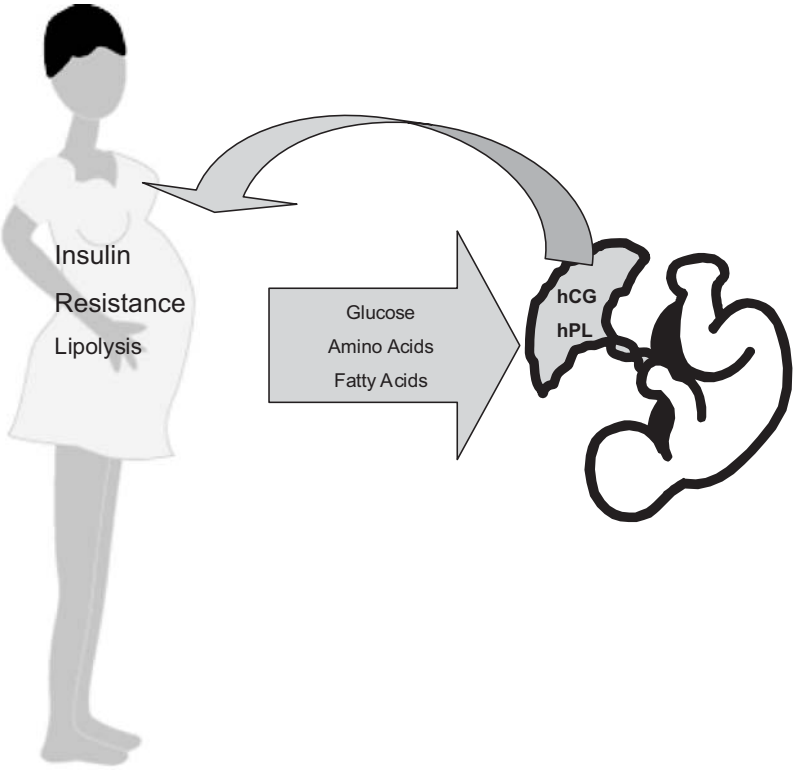

Figure 1.1 Schematic representation of maternal adaptation to pregnancy.

in fasting maternal glucose, increased maternal plasma free fatty acids, increased insulin secretion from the pancreas, but insulin resistance and reduced maternal glucose uptake to facilitate transfer to the fetus. Despite its structural similarity, hCS has little growth-promoting and lactogenic activity in humans, and normal pregnancies occur in the near absence of hCS, suggesting that hCS is not essential for pregnancy but serves a redundant function for hGH and prolactin.

Placental GH occurs in nonglycosylated and glycosylated forms and increases six- to eightfold in maternal plasma in the second trimester, replacing normal pituitary GH in the maternal circulation. In transgenic mice, overexpression of hPGH causes severe peripheral insulin resistance [44]. Placental GH may also stimulate IGF-1 production in maternal liver. Insulin resistance in pregnancy is associated with maternal islet cell hyperplasia and may be affected by hCS and placenta GH, which reduce insulin receptor number and glucose transport in insulin-sensitive tissues. In Figure 1.1, the interaction among placental hormone release, maternal metabolic state, and placental function is illustrated.

Role of adipokines

The term *adipokines* includes leptin, adiponectin, tumor necrosis factor–alpha (TNFα), interleukin-6 (IL-6), resistin, and other mediators. These are produced by many cell types including the placenta, making difficult the dissection of the roles of maternal versus placental synthesis and paracrine versus endocrine action.

TNFα, in addition to monocytes, macrophages, and adipocytes, is produced by the placenta. In obese individuals, there is a positive correlation between TNFα levels, hyperinsulinemia, and body mass index (BMI) [45]. TNFα increases insulin resistance when added to human skeletal muscle cells in culture [46]. This may be due to increased phosphorylation of IRS-1 [45] and reduced insulin receptor tyrosine kinase activity [47].

Adiponectin is synthesized only in adipocytes and possibly placenta. Adiponectin expression and secretion from white adipose tissue decrease with advancing gestation [48] and correlate with whole-body insulin sensitivity. Adiponectin acts as an

endogenous insulin-sensitizing hormone through receptors on skeletal muscle, where it stimulates glucose uptake, and liver, where it reduces uptake via adenosine monophosphate-activated protein kinase alpha (AMPK α).

Leptin, the product of the *LEP* gene, was originally described in the adipocyte and thought to modulate satiety and energy homeostasis. It is now known to be synthesized in other tissues including the placenta and to assume other roles. Serum leptin concentrations increase throughout human gestation, beginning to rise in the first trimester and correlating with hCG levels. Therefore, leptin alterations are seen before changes in body weight, suggesting another mechanism of regulation [49]. However, serum leptin levels correlate to maternal adiposity rather than placenta mass. Both leptin and leptin receptors are found in syncytiotrophoblast and will stimulate hCG secretion [50].

Placental growth factors

The placenta is also a major source of growth factors and their binding proteins that affect placental and fetal growth and development. Of these IGF-1 and -2 are the most important mediators of fetal growth. The *Igf1* and *Igf2* genes are expressed in many fetal and placental tissues where the proteins have metabolic, mitogenic, and differentiative actions and may act as local growth regulators [51]. In addition, the IGFs appear to have a role in trophoblast invasion [52]. Umbilical levels of IGFs are correlated to birth weight in many species, including humans [53], with IGF-2 concentrations being up to 10-fold higher than IGF-1. Placental IGF-2 mRNA was also positively correlated with placental weight in a group of normal and diabetic pregnancies [54]. *Igf2* is an imprinted gene expressed from the paternal allele in the placenta [55] and is expressed in syncytiotrophoblast and invasive trophoblast [56]. Deletion of either *Igf1* or *Igf2* genes results in fetal growth restriction, but deletion of the IGF type 1 receptor gene results in a more severe growth restriction, suggesting that both IGFs act through the type 1 receptor. Conversely, fetal growth is enhanced by overexpression of IGF-2 or deletion of the IGF type 2 clearance receptor [57]. In the mouse, manipulation of the *Igf2* gene reduces placental growth by 30% to 40%, involving all cell types in *Igf2*-null mice [58] or just the labyrinthine trophoblast in a placenta-specific knockdown of the *Igf2* gene [59], whereas overexpression of IGF-2 increases placental growth. In cultured human trophoblast, both IGF-1 and -2 alter glucose and amino acid transport, and in sheep, IGF-1 administration alters feto-placental protein and carbohydrate transfer and metabolism [60]. Placental System A transporter activity is increased in the placental-specific *Igf2* mutant mouse, perhaps as a compensatory mechanism, and passive diffusion is reduced [59]. Thus, the promotional effect of IGF-2 on fetal growth may be an indirect one mediated through the placenta through the IGF type 1 receptor.

The level of nutrients appears to regulate IGF concentrations in the fetus because reducing both nutrients and oxygen lowers IGF-1, although to a greater extent than IGF-2 [61]. Conversely infusion of insulin or glucose increases IGF-1 in the fetus of fasted sheep [34]. Nutritionally sensitive hormones including insulin, thyroxine, and glucocorticoids affect IGF concentrations in the fetus [62], again with deficiency affecting IGF-1 more than IGF-2. Insulin and IGF-1 levels are positively correlated in the fetus and appear to act synergistically to enhance accumulation of glucose and amino acids in the fetus [62]. Glucocorticoids affect both *Igf1* and *Igf2* gene expression in a tissue-specific manner in the fetus [63]. Hence, placental glucocorticoid metabolism may affect fetal growth in a gestational specific manner.

IGF bioavailability is regulated by expression of the IGF binding proteins (IGFBP), of which there are at least six functionally redundant isoforms, with IGFBP-1 through -4 being found in humans. Changes in IGFBP expression modulate IGF levels and thus fetal growth and are sensitive to nutritional and endocrine regulation [61]. The placenta also expresses all the IGFBPs, with IGFBP-1 being predominant. They show differential localization, with IGFBP-3 being found on the microvillous and basal trophoblast membranes and IGFBP-1 predominantly found on the fetal-facing basal surface [64].

Nutrient partitioning across the placenta

Although it is well accepted that maternal nutritional status, diet, and body size are closely correlated with birth weight, fetal nutrition is clearly not equivalent to maternal nutrition because the intervening placental syncytiotrophoblast (ST) constitutes a distinct barrier between the two circulations. The ST is a syncytial, polarized, epithelial cell layer separating the maternal

blood in the intervillous space from the fetal capillary. The ST forms by fusion of underlying cytotrophoblast cells and is composed of an apical plasma membrane or microvillous membrane (MVM) facing the maternal blood and a basal plasma membrane (BM) toward the fetal capillary. The syncytial cell layer thins in the terminal villous region, and the total transporting distance at term is 10 microns. This short transport distance between the two blood supplies allows for rapid transfer of small hydrophobic molecules and blood gases. Larger hydrophilic molecules require specialized transporting systems in the epithelial membranes to provide adequate support for fetal growth.

Fetal blood sampling and the use of stable isotopes in human pregnancy have allowed for description of maternal and fetal nutrient concentrations [65]. These recent advances have established that glucose concentrations are lower in fetuses and change in parallel to maternal levels. Amino acids are significantly higher in fetal plasma than their mothers' plasma, with glutamate being the only exception. Fatty acids on the whole are much lower in fetal than in maternal circulation. A preferential transfer of essential long-chain polyunsaturated fatty acids (LCPUFA) such as docosahexaenoic acid (DHA) and arachidonic acid across the placenta to the fetus [66] ensures adequate supply for brain and retinal development.

The cellular mechanisms for transport of key nutrients across the human placental ST have been described in detail and recently reviewed [67, 68]. The key features can be summarized as follows.

Glucose is transported across the placenta by facilitated diffusion. Abundant expression of the glucose transport protein isoform 1 (GLUT1) on the MVM allows for rapid uptake into the ST from the maternal circulation. A concentration gradient toward the fetus allows for continuous transport to the fetal circulation and maintains fetal glucose levels that mirror but never exceed those in the maternal compartment.

Active transport allows for fetal accumulation of amino acids in concentrations considerably higher than those found in maternal blood in both mid- and late gestation. The use of the sodium gradient to drive amino acid transport into the ST on the MVM, followed by passive diffusion out of the cell toward the fetus, constitutes one important mechanism for amino acid accumulation in the fetal compartment.

Circulating maternal triglycerides (TG) in very low-density lipoproteins (VLDL), as well as both chylomicrons and TG bound to albumin, are hydrolyzed by lipase enzymes in the MVM of the placental epithelium. This liberates free fatty acids for uptake by the epithelial cell. Preferential binding of LCPUFA by a placental-specific fatty acid binding protein (FABPpm) allows for specificity of transfer of these crucial cellular components.

Vectorial transport of calcium to the fetus is accomplished by influx of calcium through a variety of channels on the MVM, cytoplasmic binding to calbindin9K and sequestration in the endoplasmic reticulum, and, finally, active transport to the fetus by calcium pumps localized exclusively to the basal plasma membrane of the ST.

Placental nutrient transport capacity and fetal growth

The placental transport capacity for a number of important nutrients has been shown to be correlated to birth weight (for review, see Sibley et al. [69]). Transport capacity for essential amino acids by System L for leucine, System y+L for lysine, and System tau for taurine and nonessential neutral amino acid transport by System A have been shown to be reduced in cases of small for gestational age (SGA) and IUGR. Increased amino acid transport capacity in the placenta of large-for-gestational-age (LGA) babies of diabetic mothers has likewise been reported. In contrast to amino acids, glucose transport capacity appears to be unchanged in the placenta of small babies. There are, however, indications that glucose transport capacity is increased in the placenta of LGA babies of diabetic mothers. Maternal circulating triglycerides are hydrolyzed by lipase enzymes at the microvillous surface of the ST, and several reports indicate alterations in hydrolase enzyme activity and expression in growth-restricted fetuses and LGA fetuses of diabetic mothers. With respect to ion transport, placental calcium pump activity has been shown to be upregulated in both SGA/IUGR and LGA babies. Taken together, these data suggest that specific regulation of placental nutrient transporter activity occurs in association with altered fetal growth, as shown in Table 1.1 (for review, see Jansson and Powell [70]).

Recently, investigations using a nutrient-restricted pregnant rodent model suggested that reductions in placental amino acid transport precede deviations in fetal growth [71]. These data have led to the hypothesis that the human placenta may act as a nutrient sensor to coordinate fetal growth with the ability of the

Table 1.1 Directional changes seen in placental transport capacity in pregnancies complicated by altered fetal growth.

	IUGR	Diabetes + LGA		
Transporter	MVM	BM	MVM	BM
System A	↓	↔		↔
Leucine	↔	↓		↔
Glucose	↔	↔	↔	
Ca 2± ATPase	–		–	
Na±/H± exchanger	↓	–	↔	–
Na± K± ATPase	↓	↔	↔	↔
Lipoprotein lipase	↓	–	↑	–

mother to provide nutrients in individual pregnancies [70]. This would allow for generation of a smaller fetus when nutrient availability was low and takes advantage of periods of nutrient abundance by producing a larger, potentially more viable fetus. Pathologies in fetal growth occur when the maternal supply of nutrients is severely disrupted, as in cases of shallow placental invasion or long-term famine, or when nutrient supply is chronically in excess, as in maternal diabetes and obesity.

Regulation of placental nutrient transport

If the ability of the placenta to transport nutrients is regulated in response to the ability of the mother to supply those nutrients, then it is logical that maternal nutritional signals would be involved in this regulation. IGF-1, insulin, and leptin have been shown to upregulate placental System A amino acid uptake in a variety of experimental systems, suggesting that maternal markers of adequate nutrition stimulate transport of nutrients to the fetus (for review, see Jones et al. [68]). Interestingly, the nature of the regulation of nutrient transport differs in early pregnancy compared with term. The placenta in early pregnancy responds to insulin by increasing glucose uptake, but the term placenta responds to insulin stimulation by increasing amino acid uptake. Other factors that indicate an inability of the maternal blood supply to deliver sufficient nutrients could include oxygen levels, cytokines, and substrates. Although the exact nature of the nutrient-sensing function of the human placenta has not been fully delineated, one intracellular signaling system may in part account for this type of regulation. The mTOR controls cell growth by initiating or inhibiting protein translation in response to amino acid availability – in particular, leucine – through its actions as a phosphatidylinositol kinase–related kinase. mTOR has been localized to the ST, and phosphorylation of downstream mediators of mTOR activity is correlated with fetal size. Inhibition of the mTOR system in placental explant cultures by rapamycin resulted in a reduction in leucine uptake, suggesting a direct link between mTOR and nutrient transport to the fetus [72].

Maternal nutrition and metabolic status in the periconceptual period are critical for successful establishment of pregnancy. The early-gestation placenta secretes a number of critical hormones that alter maternal metabolism and cardiovascular and renal physiology to allow for maintenance of the pregnancy. The developing placenta appears to respond to maternal metabolic status, nutrient levels, and/or placental blood flow to regulate nutrient delivery to the fetus. These events lead to a careful coordination between maternal mobilization of nutrient stores, delivery of those nutrients to the placenta by altering maternal blood flow dynamics, and transport across the placental epithelial barrier to the fetus. The successful integration of these three diverse systems through maternal/placental/fetal endocrine signaling networks defines the ultimate pregnancy outcome – a normally grown, healthy fetus with low risk for adult disease.

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