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FETAL NUTRITION

Frederick C. Battaglia and Giacomo Meschia

Departments of Pediatrics and Physiology, University of Colorado School of Medicine, Denver, Colorado 80262

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INTRODUCTION

A review of fetal nutrition must of necessity consider such topics as fetal metabolism, placental transport and metabolism, and maternal nutrition and metabolism. In order to cover in some depth the topic of fetal nutrition without inordinately lengthening this review, we have imposed upon it certain limitations. Firstly, we limit the scope to fetal nutrition without extending excessively into areas of metabolism or placental function. To perinatal physiologists, fetal nutrition has a precise meaning, referring to the supply of nutrients delivered into the fetal circulation from the placenta. Thus, it refers to the *net* quantities of nutrients that enter the umbilical circulation, not to unidirectional fluxes, which may be of equal magnitude in either direction across the placenta. Such a definition also excludes the fluxes of nutrients into

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and out of the amniotic or allantoic fluids. Although these fluxes may be important for the establishment of the maturational sequence of certain fetal organs such as the kidneys or gastrointestinal tract, they are of little significance nutritionally in contributing net quantities of carbon, nitrogen, and other elements for growth and maintenance of the organism.

The net uptake of nutrients by the fetus is synonymous with the umbilical uptake of nutrients and implies that fetal nutrition can be separated conceptually from placental or uteroplacental nutrition. The actual developmental period implied by the term "fetal" nutrition is less precisely defined. Fetal development is encompassed by the end of embryologic development and the beginning of neonatal or postnatal development. The latter is clearly demarcated by the delivery of the newborn infant. The onset of fetal development is imprecisely defined as that stage of in utero development when recognizable organs and structures appear.

There has been some confusion introduced in perinatal biology by a lack of precision with language. The term "conceptus" has both biologic and experimental validity when it is applied to early development since the embryo and the embryonic membranes can be isolated as a unit for study in vitro. However, in fetal life placentation prevents isolation of the "conceptus", i.e. the fetus plus fetal placental tissues. Current experimental techniques do permit the isolation of the fetus from all other tissues within the uterus. Thus, fetal nutrition can be studied. One can also study the uptake of nutrients by the entire uterus and its contents. The methodology section below covers this topic in more detail. By measuring uptake of nutrients to the entire uterus and to the fetus simultaneously, we can estimate from the difference in these values the apparent uptake of nutrients by the uteroplacental tissues. Since such an estimate includes myometrium and other nonplacental structures, this is not equivalent to the placental nutritional requirements. In summary, for fetal mammalian development, the nutritional requirements of the placenta or the "conceptus" cannot be assessed precisely by any current experimental techniques.

There have been several reviews of fetal metabolism in the last 10 or 15 years. Recently, we also edited a book that covers placental as well as fetal metabolism in some detail (4). For these reasons, the current review focuses on contributions made in the 1980s to an understanding of fetal nutrition.

METHODOLOGY

In recent years there has been increasing recognition of the importance of chronic, unstressed preparations for the study of fetal metabolism. Chronic preparations are now used almost exclusively in the study of uterine and fetal metabolism in sheep (4). Progress has also been made in the development of

chronic preparations in other species (7, 38, 41, 85, 86, 93, 102). Nevertheless, the study of fetal metabolism in small mammals is still hampered by the lack of suitable techniques for observing the fetus under normal physiologic conditions.

Methods based on the Fick principle have been used extensively to measure the uptake of metabolic substrates by the pregnant uterus and the fetus. The Fick principle is the law of conservation of matter as it applies to the metabolic exchange between an organ and its circulation under steady-state conditions. For example, for fetal glucose uptake the quantity of glucose carried to the fetus by umbilical venous blood must equal the net glucose flux into the umbilical circulation from the placenta plus the glucose carried back to the placenta via umbilical arterial blood. This statement translates into the standard Fick equation:

$$\dot{Q} \text{ glucose} = f(v - a) \text{ glucose},$$

where $\dot{Q}$ glucose is the fetal glucose uptake via the umbilical circulation (mg/min), f is umbilical blood flow (ml/min), and $(v - a)$ glucose is the venous-arterial concentration difference of glucose across the umbilical circulation (mg/ml). Thus, fetal uptake is calculated from simultaneous measurements of flow and venous-arterial concentration differences.

There are numerous technical and conceptual problems related to the application of the Fick principle (4). A relatively common mistake has been to calculate uptakes by multiplying blood flow times plasma concentration arteriovenous differences. Implicit in this calculation is the assumption that whole-blood and plasma concentrations are equal. For several metabolites, this assumption can introduce a large error. A more fundamental source of error is that most analytical methods cannot adequately measure whole-blood arteriovenous differences that are less than 5% of the arterial concentration and are unable to detect a difference of $<2\%$. Therefore, the absence of a statistically significant arteriovenous difference is not proof that there is no metabolically important flux (4).

An interesting problem in the application of the Fick principle is that metabolic interconversions may obscure the meaning of an arteriovenous difference, even if this difference is accurately measured. This has been clearly demonstrated by studies of lipid metabolism. A recent study of lipid transfer across the guinea pig placenta artificially perfused via the umbilical circulation showed that nonesterified fatty acids were transported from maternal blood into the umbilical perfusate despite the absence of a net uptake of nonesterified fatty acid by the pregnant uterus (110). This observation was explained by demonstrating that the placenta rapidly hydrolyzes triacylglycerol molecules carried by the maternal circulation. As a consequence, the arteriovenous difference of free fatty acids across the uterine circulation

represents the algebraic sum of fatty acid uptake and fatty acid production by the placenta.

Furthermore, the umbilical uptake of nutrients is not synonymous with their rate of fetal utilization. Often the net flux of a substrate from placenta to fetus is less than the rate of utilization of that substrate by fetal tissues. For example, if some of the glucose utilized by the fetus is derived from fetal glycogenolysis and/or glucogenesis, fetal glucose utilization exceeds fetal glucose uptake via the umbilical circulation. Nevertheless, the net umbilical uptake of glucose is part of the net flux of nutrients from placenta to fetus and, as such, has unique interest nutritionally, regardless of whether it is equal to or less than fetal glucose utilization.

Tracer methodology is being used with increasing frequency for studies of placental and fetal metabolism. The wide use of tracers has raised methodological issues that must be understood for a correct interpretation of the recent literature. An issue of basic importance has been the physiological meaning of fetal turnover measurements. To measure fetal CO_2 turnover, for example, investigators infused ^{14}C-labeled bicarbonate at a constant rate into a fetal vein and measured fetal arterial CO_2 specific activity at steady state (1, 111). Turnover was calculated as the ratio of infusion rate to specific activity. Similarly, tracer infusion and fetal blood specific activity measurements were used to calculate the fetal turnover of glucose (2, 113), lactate (108, 113), fructose (78, 113), and several amino acids (75, 82, 92, 98, 112). In some instances investigators interpreted these turnover numbers as a measure of fetal metabolic activity.

However, measurements of tracer concentration and specific activity in umbilical arterial, umbilical venous, maternal arterial, and uterine venous blood have shown conclusively that the exchange of tracer and tracee molecules between fetal blood and placenta and between placenta and maternal blood is an important component of fetal turnover for most metabolites. This is particularly striking for the turnover of CO_2. Only one fifth of fetal CO_2 turnover represents the metabolic production of CO_2 by the fetus (111). The remainder represents the random exchange of CO_2 molecules between the fetal CO_2 pool and the large maternal-placental CO_2 pool. Similarly, when ^{14}C-labeled glucose was infused into a limb vein of the fetal lamb and the net loss of tracer into placenta and mother was measured (56), the placenta took up approximately 53% of the infused labeled glucose and transferred approximately 24% to the mother. Thus, fetal glucose utilization was only 47% of fetal glucose turnover. Its utilization could be calculated from the equation

$$\text{Glucose utilization} = \frac{\text{tracer infusion rate} - \text{net tracer loss via the placenta}}{\text{fetal arterial specific activity}}$$

General recognition of the fact that for many substrates fetal turnover measurements do not define fetal metabolic activity has generated considerable interest in a steady-state, two-pool model of maternal-fetal exchange (59, 101). According to the original interpretation of this model, the simultaneous infusion of two glucose tracers into the maternal and fetal circulations, combined with measurements of the specific activities of maternal and fetal tracers in maternal and fetal arterial blood, allows the calculation of maternal glucose utilization, net fetal uptake of maternal glucose, fetal glucogenesis, and fetal glucose utilization. The investigators who first applied the two-pool model believed that the net fetal uptake of maternal glucose thus calculated was, in fact, the net fetal uptake of glucose via the umbilical circulation (59). However, subsequent experiments in which the results of the two-pool model calculation were compared with direct measurements of fetal glucose uptake and utilization showed that the "net fetal uptake of maternal glucose" calculated by the model was almost twice the fetal uptake of glucose via the umbilical circulation. Similarly, the calculated fetal utilization exceeded the actual utilization by approximately 60% (56).

These discrepancies exist because the two-pool model does not take into consideration placental glucose utilization, which in sheep is very high. In the two-pool model the glucose utilization by the whole system (i.e. mother + placenta + fetus) is partitioned between mother and fetus so that some of the glucose utilized by the placenta is included in the calculation of fetal glucose uptake and utilization. This is a consequence of the fact that the placenta takes up and utilizes glucose molecules from both its maternal and fetal surfaces.

In a recent paper (3), the information provided by the two-pool model of maternal-fetal glucose exchange was given a new interpretation. According to this viewpoint, what the model first interpreted as "fetal glucose utilization" should now be interpreted as glucose utilization by the fetus plus the "fetal placenta," the latter being placental tissues that utilize exclusively glucose molecules derived from the fetal glucose pool. Fetus plus "fetal placenta" would constitute the conceptus. It is important to note, however, that there is no experimental validity to the concept of a homogenous fetal glucose pool since experiments of glucose tracer infusion into the fetus have shown that the fetal surface of the placenta is exposed to a marked specific activity gradient of glucose from arterial to venous end of the placental circulation as unlabeled maternal glucose molecules enter fetal blood (56). Therefore, the concept of a "fetal placenta" that derives glucose from a homogeneous fetal glucose pool seems implausible.

The CO_2 produced by the fetal lamb in the oxidation of metabolic substrates such as glucose has been estimated by applying the Fick principle to the rate of $^{14}CO_2$ excretion via the umbilical circulation during the constant infusion of the ^{14}C-labeled substrates into a fetal limb vein (54, 78, 112). This technique does not require the measurement of fetal CO_2 specific

activity and provides fairly accurate data because the rapid exchange of CO_2 between placenta and fetal blood creates a relatively large arteriovenous difference of $^{14}CO_2$ across the umbilical circulation. It is important to take into consideration the role of placental metabolism for a proper interpretation of fetal $^{14}CO_2$ excretion measurements. For example, a fraction of the ^{14}C-labeled glucose infused into the fetus enters the placenta and is converted into ^{14}C-labeled lactate (108) and fructose (78) molecules. Some of these molecules enter the fetal circulation and are oxidized within the fetus. Therefore, placental metabolic activity contributes to the rate of CO_2 production from fetal glucose molecules.

CARBOHYDRATES

Research in several species has established the quantitative importance of glucose as a fetal and placental nutrient. Measurements of arteriovenous concentration differences across the uterine and umbilical circulations have shown that the placenta takes up glucose from maternal blood and releases it into the umbilical circulation (4, 77). The quantity of glucose delivered into the umbilical circulation is less than the quantity taken up from the uterine circulation; this reflects the fact that the placenta uses glucose as a metabolic fuel (4).

To quantitate the importance of glucose as a fetal nutrient, fetal glucose uptake via the umbilical circulation has been compared with fetal oxygen uptake and with fetal carbon requirement. The latter has been estimated by adding the amount of fetal carbon accretion due to growth to the amount of carbon excreted by the fetus in the form of CO_2, glutamate, and urea carbon (4). In well-nourished sheep, the fetal intake of glucose via the umbilical circulation would be sufficient to satisfy approximately half of fetal oxygen consumption if all the glucose were converted to CO_2 and water, and it represents approximately one fourth of fetal carbon requirements (4). In relation to oxygen demands, the umbilical uptake of glucose by the human fetus appears to be somewhat larger than in sheep (80). This larger uptake may be related to the fact that the near-term human fetus has a brain mass approximately eight times larger than a sheep fetus of comparable body weight. Under normal physiologic conditions, glucose is the main substrate of cerebral oxidative metabolism in prenatal as well as postnatal life (8, 94, 95). In addition to the brain, other fetal organs have been studied in relation to their nutritional requirements (12, 20, 42, 43, 63, 64, 106). Of particular interest is the finding that the fetal heart utilizes mainly glucose and lactate (37, 114). This is in sharp contrast to the adult heart for which fatty acids and amino acids are the most important metabolic fuels.

From the viewpoint of the nutritional requirements of pregnancy, the uptake of metabolic substrates by the pregnant uterus is more important than

fetal uptake alone. In the past the distinction between metabolic needs of the pregnant uterus and of the fetus alone was not emphasized because the metabolic needs of the fetus were thought to be much greater than those of the uterine tissues and placenta, especially in the last third of pregnancy. However, studies in sheep have conclusively demonstrated that this is not the case, especially in relation to glucose requirements (76). Near term, approximately 30 to 40% of the glucose taken up by the pregnant uterus is delivered to the fetus, while the remainder is utilized by the uteroplacental mass (76, 78). The ovine uteroplacenta uses glucose as fuel for its oxidative metabolism. In addition, it produces lactate (76, 84, 108), which is delivered into both the uterine and umbilical circulations, and fructose (78), which is delivered exclusively into the fetal circulation. The amount of lactate delivered by the placenta to the fetus has been quantitated by applying the Fick principle to the umbilical circulation; this is possible because the lactate flux creates a measurable venous-arterial concentration difference (108). Quantifying the net fructose flux from placenta to fetus has been much more difficult because the concentration of fructose in ovine fetal blood is high and does not allow the detection of a metabolically significant flux by means of venous-arterial difference measurements. However, tracer studies have shown that the ovine fetus utilizes fructose rather slowly in comparison to glucose and that the production rate of CO_2 is approximately five times greater from fetal glucose carbon than from fructose carbon (54, 78).

A schematic representation of glucose, lactate and fructose net fluxes between maternal blood and uteroplacenta and between uteroplacenta and fetus is presented in Figure 1. Information as detailed as that shown in Figure 1 is available only for late-gestation sheep. Some progress has been made in extending the study of uteroplacental and fetal metabolism to mid-gestation sheep (5). Furthermore, data about the uptake of nutrients by the pregnant uterus have been collected for horses (102), cattle (34), pigs (38, 93), rabbits (41, 67), and guinea pigs (10, 85, 86). In agreement with the data in sheep, these studies demonstrate a large uterine glucose uptake concomitant with the release of lactate. The human placenta perfused in vitro has also been shown to metabolize glucose and release lactate (50).

Several studies have focused on the factors that control the fetal uptake and utilization of glucose. Under normal physiologic conditions, the concentration of glucose in fetal blood is less than in maternal blood. The maternal-fetal gradient drives maternal glucose into the fetus. If the magnitude of the gradient is decreased, either by maternal hypoglycemia or by fetal hyperglycemia, the flux of glucose into the umbilical circulation decreases (58, 103). Within a small range of glucose concentrations, the relationship between glucose gradient and placental glucose transport is linear (58). However, placental glucose transport is mediated by saturable carriers (7, 51, 66, 103,

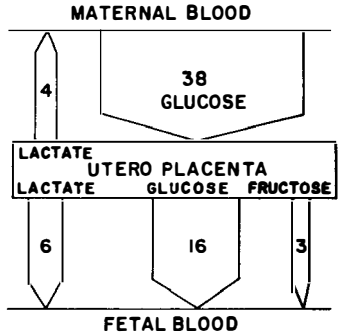

Figure 1 Representative normal values for net fluxes (mg/min) of glucose, lactate, and fructose between maternal blood, uteroplacenta, and fetal blood in a ewe carrying a 3-kg fetus.

115). The affinity of these carriers appears to be relatively small in relation to normal blood glucose concentrations, but its numerical value has not been clearly defined.

For any given transplacental glucose concentration gradient, the placental-to-fetal glucose transfer rate depends on the area available for transfer. Occlusion of placental vessels (25) and conditions that impede placental growth (6, 96) result in fetal hypoglycemia and a reduced glucose transfer rate. A question of considerable interest is what role maternal and fetal insulins play in the regulation of placental glucose uptake and transport. The placenta is endowed with insulin receptors on the maternal surface of the trophoblast (29), which suggests that insulin controls placental glucose uptake. Earlier studies (28) seemed to indicate that an increase in maternal insulin concentration increases the rate of placental glucose transfer into the fetus. However, subsequent studies have shown that the infusion of insulin in either maternal or fetal blood does not change significantly the rate of placental glucose uptake and transport as long as maternal and fetal glucose concentrations are kept constant by means of a "glucose clamp" technique (16, 55, 109). An important implication of these studies is that pregnancy entails a marked change in the maternal regulation of glucose, for they indicate that the growth in glucose demands accompanying placental and fetal growth increases the mass of tissues that are largely insensitive to insulin regulation. Simultaneous measurements of maternal glucose production and uterine glucose uptake in late-gestation sheep have demonstrated that uterine uptake claims a large fraction of maternal glucose production (57, 83).

Although placental glucose transport and utilization seem to be insensitive to acute changes in insulin concentration, the utilization rate of glucose by the fetus is under the control of fetal insulin (9, 14, 39, 40, 52, 53, 79, 88–91).

AMINO ACIDS

Growth involves the accretion of a net quantity of protein, underlining the importance of amino acids as nutrients in fetal life. The umbilical uptake of amino acids is the primary nutritional supply line for these compounds during fetal life. In the 1970s a good deal of research centered around describing the umbilical uptake of amino acids under various conditions in the fetal lamb (61, 69). Thus far, no other mammalian species has been studied in terms of the umbilical uptake of amino acids. However, a number of characteristics of amino acid uptake described in the fetal lamb have been confirmed in other species using indirect techniques.

From a nutritional viewpoint, the role amino acids play in fetal nutrition has the following characteristics:

1. The quantity of amino acid provided to the fetus exceeds its rate of accretion in tissue protein (13, 61, 68–71, 75, 82, 98, 99).
2. Amino acids are used as fuels by the fetus, as evidenced by (*a*) the demonstration of fetal $^{14}CO_2$ production after the fetal infusion of ^{14}C-labeled leucine, lysine, tyrosine, and alanine (49, 82, 98, 112); and (*b*) the high rate of urea production within the fetus (46, 47).
3. Several neutral amino acids are delivered to the fetus in large excess compared to their net rates of accretion, whereas there is no net transfer of the acidic amino acids glutamate and aspartate from the placenta into the fetal circulation. Thus, these amino acids must be synthesized within the fetus. In fact, there is a net transfer of glutamate from the fetal circulation into the placenta (61, 69).

Interorgan Cycling of Amino Acids Between the Placenta and Fetal Liver

One of the first suggestions that the placenta plays a unique role in the accretion of nitrogen by the fetus came with the demonstration that there is a net ammonia production by the placenta, which is then delivered into both the uterine and umbilical circulations. More recently there have been further studies suggesting a high ammonia production rate by placentas other than the sheep placenta (60, 62). In addition, the ammonia produced in the placenta, a fraction of which is taken up in the umbilical circulation, is extracted by the fetal liver, which also has a large net uptake of amino acids from the umbilical venous blood (74). The role of placental amino acid metabolism in effecting transformation of substrates provided to the fetus is also supported by the observations of Palacin et al (84), who demonstrated significant placental production of ^{14}C-lactate from ^{14}C-alanine in the rat placenta. Thus, the large placental production of lactate under aerobic conditions is not entirely

attributable to metabolism of glucose, although ^{14}C-lactate production from ^{14}C-glucose within the sheep placenta has been clearly demonstrated under in vivo conditions (103).

The relatively high activity of the branched-chain amino transferases found in the human and sheep placentas (45, 65) suggests considerable metabolism of the branched-chain amino acids to their corresponding alpha-ketoacid derivatives. The question of how protein synthesis within the placenta and amino acid transport across the placenta are linked is not resolved. The studies of Gusseck et al (48) of human placental fragments in vitro suggested that there was no such link, whereas Carroll & Young (13) studying the perfused guinea pig found transport of amino acids was decreased by adding cyclohexamide to the perfusate. It is clear that the free amino acid pool within the placenta cannot be treated as a single homogenous pool regardless of whether entry represents amino acids released by protein breakdown or from the maternal circulation.

Amino Acid Accretion

During fetal life there is a marked decrease in the proportion of body weight represented by visceral organs compared to carcass (i.e. skeletal muscle, connective tissue, bone, and cartilage). In addition, within each tissue type there are changes reflecting increasing cellularity and decreasing intercellular matrix. From a nutritional viewpoint these changes lead to a change in the amino acid composition of the body proteins as gestation advances, changes that translate into specific but different rates of accretion for each amino acid. Furthermore, there are differences among species in these accretion rates (75, 107). This is important in comparing the supply of amino acids coming from the placenta to the rate of accretion, but it is also an important characteristic to bear in mind as more frequent attempts are made to estimate protein synthetic rates in fetal life because these estimates are usually made by determining the flux rate of a single amino acid into protein synthesis and multiplying this flux by the proportion that amino acid represents in body proteins. Assumptions of this proportion based upon measurements in adult life or even in fetal life at a very different gestational age and/or in other species will lead to errors in the calculated protein synthetic rate (68).

During maternal fasting or starvation there are no accurate methods to determine the rate of accretion of fetal amino acids over a relatively short time span. Therefore, comparisons of fetal amino acid accretion and uptake during maternal fasting are of questionable validity.

Fetal Swallowing of Amniotic Fluid

One of the mechanisms regulating amniotic fluid volume is fetal swallowing. Any pathology that interferes with this process in a major way leads to polyhydramnios. There has been considerable speculation about the role in

fetal metabolism of amniotic fluid nutrients swallowed and absorbed through the fetal gastrointestinal (GI) tract. Sagawa et al (97) have shown that as early as the sixth month of pregnancy the intestinal transport systems for sugars and amino acids are well developed in the human fetus. Thus, it is not surprising that Charlton et al (18–20) were able to demonstrate an apparent reduction in the degree of fetal growth retardation by the intragastric infusion of nutrients into the fetus. These were the equivalent animal studies to the several clinical attempts that have been made to correct intrauterine growth retardation in humans through the intraamniotic infusion of nutrients (18–20).

Attempts to improve fetal nutrition by infusion of nutrients into the amniotic fluid relying upon fetal swallowing for absorption and digestion will continue. However, this should not be construed as representing a normal avenue of fetal nutrition. The latter is represented solely by the umbilical uptake of nutrients from the placenta. Although there is a turnover of nutrients in amniotic fluid during gestation, amniotic fluid is not the source of the net carbon and nitrogen accretion required for growth. In fact, where estimates of portal uptake of nutrients have been made (20), there is clearly a net consumption of nutrients by the fetal GI tract rather than a net absorption. The impact of maternal fasting and starvation upon the nutritional state of the fetus, including the status of amino acids, is discussed below.

Amino Acid Transport and Pathologic States

A number of studies have attempted to demonstrate an effect of maternal ethanol ingestion upon fetal uptake of amino acids in primates, sheep, rats, and in the human placenta in vitro (35, 36, 73). The many technical and design problems with these studies preclude a conclusion that ethanol ingestion per se reduces the total quantity of amino acids delivered to the fetus, but the studies are consistent in suggesting an alteration in the placental uptake of amino acids from the maternal circulation upon maternal ethanol ingestion.

In studies of the effect of chronic maternal hyperglycemia upon the transfer of nutrients to the fetus, the hyperglycemia had no demonstrable effect upon alanine transport (91). Clinically, Cetin et al (15) described a significant reduction in umbilical venous plasma amino acid concentrations among intrauterine growth retarded (IUGR) infants compared to appropriately grown infants. Furthermore, at any given maternal concentration there were significantly lower concentrations for the sum of the branched-chain amino acids in the IUGR infants.

FATS AND LIPIDS

There has been remarkably little research directed toward the nutritional supply of lipids, free fatty acids (FFA), and ketoacids to the fetus from the placenta and maternal tissues. Certain general characteristics of fetal growth

and of placental transport established in the past bear on the question of the nutritional supply from the placenta versus the carbon requirements for growth and fat deposition. It is now well established that in those species whose placentas are relatively impermeable to free fatty acids, the fetuses are born with very little body fat (for examples, the pig and sheep). However, the converse is not always the case. Some species whose placentas are more permeable to free fatty acids have newborns with a relatively high fat concentration (human and guinea pig), while others have newborns with little body fat (rat and rabbit). In general, epitheliochorial placentas (e.g. sheep, cow, and pig placentas) are relatively less permeable to free fatty acids than hemochorial placentas (e.g. human, rabbit, and guinea pig placentas).

Recently, Elphick & Hull (33) studied the cat placenta, which is a hemoendothelial placenta, and found it relatively impermeable to free fatty acids. Booth et al (11), working with the perfused human placenta, reported that there was no difference in the transfer rates of palmitic and linoleic acids across the placenta and concluded that there was no selectivity in the transfer process. Goldstein et al (44) showed that there was a marked increase in the content of the essential fatty acid linoleate in the fetal tissues associated with maternal diabetes. The increase in linoleate content within fetal tissues was directly proportional to the triglyceride accumulation in the conceptus. Their observations that the increase in linoleic concentration was most marked in fetal liver suggests a unique role for this organ in the uptake of fatty acids entering from the placenta. This would be similar to the interorgan cycling of amino acids between fetal liver and placenta (74). In the rabbit and guinea pig, metabolic balance studies across the uterine circulation in pregnant animals support the role of fats in providing a substantial fraction of the carbon requirements of the conceptus (10, 41, 67, 85).

An important contribution was made to the nutritional implications of the transfer of essential fatty acids across the placenta by a series of publications by Clandinin et al (21–24). They described the accretion rate of omega-6 and omega-3 fatty acids both in brain tissue and other tissues of the human fetus. Their data point out that the storage of these compounds in fetal liver could supply adequate quantities of these fatty acids for brain growth for only a very limited time (i.e. 2–3 days for the omega-3 fatty acids in premature babies). It is not clear whether chain elongation and desaturation of linoleic acid ($C_{18:2}$, omega-6) and linolenic acid ($C_{18:3}$, omega-3) occur in the placenta and/or fetal liver since the conversion of linoleic acid to arachnidonic acid ($C_{20:4}$, omega-6) has been the only conversion demonstrated in the human placenta.

While the link between placental permeability to free fatty acids and the body composition of the infant has been reasonably well studied, there have been fewer studies on the role of the placenta both in the uptake and transport of complex lipids and in the transformation or metabolism of lipids within the

placenta (26). This topic is very important now that the very high metabolic rate of the placenta has been established as well as its key role in transforming nutrients taken up from the maternal circulation prior to entry into the fetal circulation. Certainly, the uptake of complex lipids by the placenta has been well demonstrated in the rabbit (32), although they are not transported intact to the fetus. The complex lipids in Intralipid® (Kabi Vitrum, Inc, Alameda, CA) do cross the placenta in the rabbit and in man (31). Elphick & Hull (33) suggested that some of the triacylglycerol found in human umbilical venous blood may have been resynthesized within the placenta prior to transport since the fatty acid composition was not identical to that in Intralipid. This is by no means a conclusive demonstration that complex lipids can be broken down and resynthesized in the placenta prior to transport, however. The breakdown of complex lipids taken up from the maternal circulation and the release into the fetal circulation as free fatty acids has been well demonstrated in several species (31, 32, 110). The placenta contains a high lipoprotein lipase activity (27). The studies in rabbits and in humans after Intralipid infusion have shown the transfer of free fatty acids into umbilical venous blood. Even in species with a relatively impermeable placenta, such as the sheep, it has been shown that during undernutrition the uptake of ketone bodies (the oxidation products of free fatty acids) is increased by the uterus, although the uptake of free fatty acids is not (17). Chandler et al demonstrated a two- to threefold increase in the net uterine uptake of ketone bodies during moderate maternal hyperketonemia (17).

UTEROPLACENTAL AND FETAL RESPONSE TO A RESTRICTION OF MATERNAL FOOD INTAKE

In the last decade there have been several studies of the effect of restricting maternal food intake upon uteroplacental and fetal sheep metabolism. Most experiments have been on the effect of complete food withdrawal for several days (57, 71, 72, 81, 87, 105), but in one experiment ewes on a standard normal diet were compared with ewes receiving approximately one third this diet (17).

These studies have shown that concomitant with the decrease in maternal and fetal plasma glucose concentration that occurs during a restriction in food intake there is a marked decrease in the uteroplacental and fetal glucose uptake and in the rate of fetal glucose utilization (17, 57, 58, 71).

In one study (58), fetal glucose utilization decreased somewhat less than uptake, which indicates that fasting may stimulate fetal gluconeogenesis. However, more direct evidence of fetal gluconeogenesis stimulation by fasting is lacking, and there are no data about the time course and exact magnitude of this response. The comparison of glucose and oxygen uptakes has

demonstrated that the decrease in glucose uptake by the pregnant uterus and by the fetus is not accompanied by a commensurate decrease in oxygen uptake, which implies a decrease in the contribution of glucose to uteroplacental and fetal oxidative metabolism (71, 72, 81, 100). This suggestion has been verified by experiments with ^{14}C-labeled glucose showing that the production rate of CO_2 from fetal glucose carbon decreases with fetal hypoglycemia, both in absolute terms and in relation to oxygen uptake (54). Fasting does not produce a profound reduction in fetal oxygen consumption. Although prolonged fasting can produce fetal growth retardation and, therefore, can reduce the rate at which fetal oxygen demands increase with gestation, oxygen uptake per kilogram of fetus remains virtually unchanged (17, 71). There is disagreement in the literature concerning the effect of fasting on placental oxygen demands. According to some evidence, fasting is accompanied by a decrease in uterine blood flow and a marked decrease in uteroplacental oxygen uptake (17, 81), whereas another study (71) failed to demonstrate a significant decrease in either variable.

The decrease in placental glucose utilization and transport during fasting is a direct consequence of the decrease in maternal blood glucose. Although maternal insulin concentration also decreases with fasting, there is no evidence that the decrease in glucose utilization and transport is causally related to decreased maternal insulin levels.

The response of uterine glucose uptake to variations in maternal glucose is likely to play an important role in the regulation of glucose during pregnancy. A comparative study of fed and fasted pregnant ewes showed that fasting caused a decrease in maternal glucose production from 150 to 71 mg/min and a decrease in uterine glucose uptake from 51 to 24 mg/min (57). Clearly, maternal tissues would have been severely deprived of glucose if uteroplacental and fetal glucose uptakes had remained constant. It is interesting to note that exercise may alter the partitioning of glucose between maternal tissues, placenta, and fetus; it may also affect the nutritional state of the mother in determining fetal glucose availability and utilization (17).

The decrease in the glucose/oxygen uptake ratio by pregnant uterus and fetus induced by maternal hypoglycemia implies the oxidation of alternate substrates. In sheep the nature of these fuels appears to be markedly different for placenta and fetus. The maternal ketonemia of undernourished ewes is accompanied by an increased uterine uptake of 3-hydroxybutyric acid (3HB) in quantities sufficient to satisfy a relatively large portion of uterine oxygen uptake (17, 87). Since no appreciable amount of 3HB is transported to the fetus, ketoacids then become an important oxidative substrate of placental metabolism alone. By contrast, the decrease in glucose availability in the fetus is compensated for by increased catabolism of amino acids. During fasting, fetal urea production increases (71, 105). Furthermore, a recent study

of fetal leucine metabolism demonstrated that fetal leucine oxidation rate increased significantly with fasting from 5.8 ± 1.0 to 10.8 ± 1.3 μmol/min (112). A question of major importance is whether this increased fetal amino acid catabolism is accompanied by an increase in the flux of certain amino acids from mother to fetus. The large error with which current methods measure uterine and fetal amino acid uptakes has precluded a definitive answer to this question (71, 81).

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