Review Article

In utero fuel homeostasis: Lessons for a clinician

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ABSTRACT

Fetus exists in a complex, dynamic, and yet intriguing symbiosis with its mother as far as fuel metabolism is concerned. Though the dependence on maternal fuel is nearly complete to cater for its high requirement, the fetus is capable of some metabolism of its own. The first half of gestation is a period of maternal anabolism and storage whereas the second half results in exponential fetal growth where maternal stores are mobilized. Glucose is the primary substrate for energy production in the fetus though capable of utilizing alternate sources like lactate, ketoacids, amino acids, fatty acids, and glycogen as fuel under special circumstances. Key transporters like glucose transporters (GLUT) are responsible for preferential transfers, which are in turn regulated by complex interaction of maternal and fetal hormones. Amino acids are preferentially utilized for growth and essential fatty acids for development of brain and retina. Insulin, insulin like growth factors, glucagon, catecholamines, and letpin are the hormones implicated in this fascinating process. Hormonal regulation of metabolic substrate utilization and anabolism in the fetus is secondary to the supply of nutrient substrates. The knowledge of fuel homeostasis is crucial for a clinician caring for pregnant women and neonates to manage disorders of metabolism (diabetes), growth (intrauterine growth restriction), and transitional adaptation (hypoglycemia).

Key words: Fetus, fuel, glucose, metabolism

Introduction

The maintenance of a balanced and continuous supply of nutrients from the mother to the fetus throughout gestation is critical in maintaining a healthy, viable, and optimally growing fetus. For many years even after oxygen was discovered by Lavoisier,[1] it was assumed that the fetus had no metabolism of its own. Now it is well understood that the placenta and fetal liver work as a coordinated multi-organ system to supply nutrients to meet fetal metabolism and growth.[2] Enormous attempts have been made subsequently to understand the fetal metabolism in a very low oxygen environment (pO_2 16-27 mmHg)—'Mount Everest *in utero*' concept.

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Estimation of fetal oxygen consumption may be used as a direct indicator of the fetal metabolism. Though the fetus has a great capacity for anaerobic metabolism using lactate, ketone bodies, amino acids effectively, the energy processes operate essentially through oxidative pathways. Based on fetal oxygen consumption, a fetus expends 55 kcal/kg/day.[3] The immense advancement in understanding fetal and perinatal fuel homeostasis is due to methodological advances in kinetic studies using stable isotopic tracers in conjunction with mass spectrometric quantification.[4]

Carbohydrate Metabolism

Glucose

The fetus has been described as a 'glucose-dependent parasite.' Carbohydrate is the primary fuel for the fetus, accounting for about 80% of fetal energy consumption. The remaining 20% of fetal energy needs is provided by lactate, amino acids, and others. Fetal glucose utilization rates (5-7 mg/kg/min) are higher than in adults (2-3 mg/kg/min). The placenta maintains a continuous uninterrupted supply *in utero*—the hallmark of fetal life—by the process of facilitated diffusion. The

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three key points in this complex regulation of fetal glucose metabolism are:[5]

1. Maintenance of maternal glucose concentration by increasing maternal glucose production and development of relative maternal glucose intolerance and insulin resistance.
2. Placental transfer of maternal glucose to the fetus, buffered by placental glucose utilization.
3. Fetal insulin production and enhancement of glucose utilization in sensitive tissues.

The fetal glucose is almost all of maternal origin and is generally 10-20 mg/dl less than maternal levels (70-80% of maternal levels). This gradient favors transfer of glucose to the fetus. Fluctuations in maternal blood glucose are rapidly reflected in parallel changes in fetal glucose concentration. Though uterine, placental and fetal glucose uptake are related to maternal glucose concentrations, the partition of uterine glucose uptake into fetal and uteroplacental glucose uptakes is regulated by fetal glucose concentrations and is *independent* of maternal glucose availability [Figure 1].[5] With increasing age and size of the fetus, the placenta successfully supplies more glucose by:

1. Increase in maternal-fetal glucose gradient as fetal glucose levels decrease due to increase in insulin dependent uptake of glucose by adipose tissue and skeletal muscle.
2. Increase in placental glucose transport (PGT) capacity by an increase of the fetal glucose transporters.

Fetal glucose transporters [Table I]

The facilitated glucose diffusion is mediated by a family of structurally similar proteins known as the glucose transporters (GLUT) encoded by a family of genes SCL2A and expressed in a tissue-specific manner [Table 1]. GLUT 1 is the dominant isoform in most fetal tissues and the placenta.[6] Basal membrane GLUT 1 is the rate limiting step in fetal glucose levels. The maternal side of the placenta has a 5-fold greater increase in GLUT 1 than the fetal side. Insulin, insulin-like growth factors (IGF), and other hormones and peptides regulate its activity and expression. GLUT 1 in the placenta are not saturated until 198-235 mg/dl maternal glucose- levels that are significantly above the usual maternal blood glucose level.[7] This may indeed be a protective mechanism from adverse effects of severe hyperglycemia. With increasing gestational age, the placental glucose transfer is enhanced by increase in GLUT 1 and GLUT 3. GLUT 3 is more efficient, has very strong affinity to glucose and may be responsible for glucose transfer at very low glucose concentrations. GLUT 4 expressions are upregulated by hypoglycemia and hypoinsulinemia in skeletal muscle and adipose tissue, in contrast to no change in the brain, and downregulated with hyperglycemia.

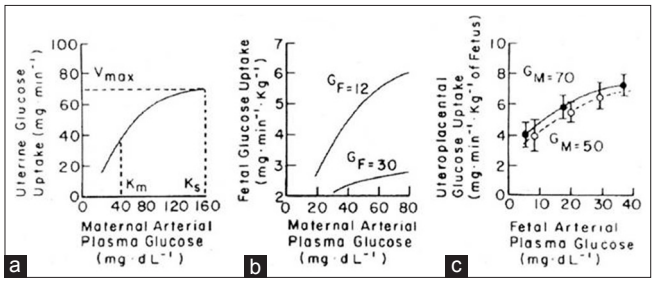

Figure 1: Uterine, fetal, and uteroplacental glucose uptake rates as functions of maternal (a, b) or fetal (c) arterial plasma glucose concentrations in pregnant sheep (reproduced from Ref 5)

Alternate fuels

The energy expenditure of the fetus as measured by oxygen consumption is 55 kcal/kg/day and the glucose uptake accounts for only 32 kcal/kg/d. Even if the supply of glucose is reduced, fetal oxygen consumption remains normal as the fetus is fully capable of using other substrates such as lactate, ketoacids, amino acids, fatty acids, and glycogen as fuel [Figures 2 and 3].[8] Routinely, approximately 40-50% of the transported glucose is used by placenta for oxidation or converted to glycogen and lactate. The fetus uses this lactate along with glucose for fat and glycogen synthesis (accretion needs). With increasing gestation, maternal lipolysis provides fuel for the mother and also gluconeogenic precursors for the fetus. Normally, gluconeogenesis and ketogenesis are not seen in the fetus when substrate supply is adequate.

Glycogen

In the third trimester, some of the energy and substrate available to the fetus are channeled from meeting needs for ongoing growth and development to energy storage.[9] The fetal liver contains the full complement of enzymes required for the synthesis

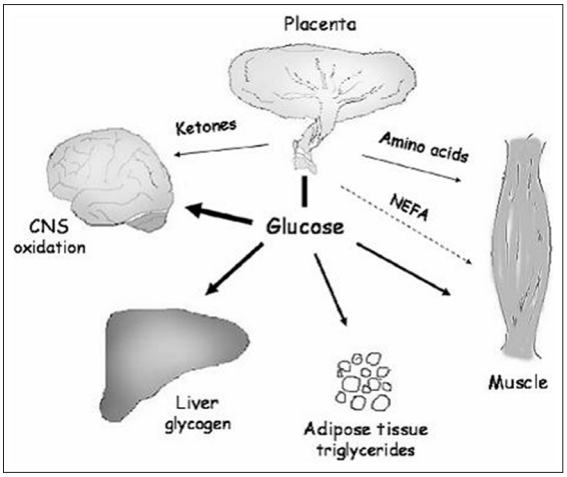

Figure 2: Energy substrates transported to and deposited in the fetus

Table 1: Distribution of glucose transporters

GLUT	Class	Primary site of expression	Affinity to glucose
GLUT-1	I	All fetal tissues, erythrocytes, brain	High affinity (+ + +)
GLUT-2	I	Liver, pancreas, intestine	Low affinity (+)
GLUT-3	I	Neurons, kidney, testis, placenta	Highest affinity (+ + + +)
GLUT-4	I	Adipose tissue, skeletal muscle, cardiac muscle	Moderate affinity (+ +)
GLUT-5	II	Small intestine, testis, kidney	Fructose uptake (+)
GLUT-6	III	Brain, spleen, leucocytes	Low affinity (+)
GLUT-7	II	Liver, small and large intestine, testis, prostate	High affinity for glucose and fructose (+++)
GLUT-8	III	Testis, brain	High affinity (+++) also fructose, galactose
GLUT-9	II	Liver, kidney, intestine	Uric acid uptake
GLUT-10	III	Ubiquitous	Unknown
GLUT-11	II	Pancreas, kidney, placenta	Low affinity for glucose, high for fructose
GLUT-12	II	Heart, prostate	Unknown
GLUT 13-14		Newer proteins–Roles to be determined	

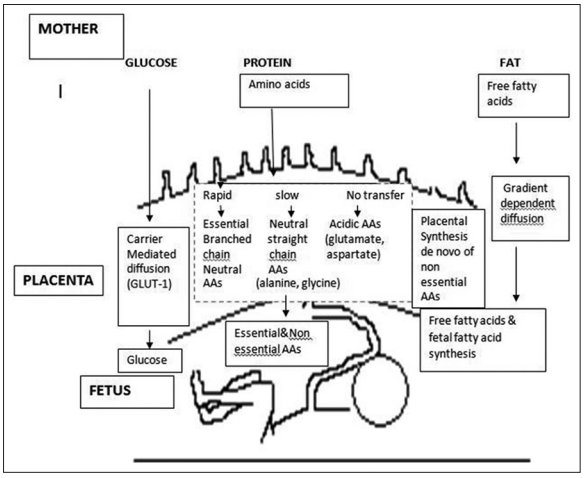

Figure 3: Energy and nutrient substrates transfer to fetus (adapted from Ref 8)

and breakdown of glycogen and is the main glycogen storehouse (2-3 times adult), followed by heart (10 times adult), and skeletal muscle (3-5 times adult). However, only the liver contains sufficient glucose-6-phosphatase for the release of glucose in the circulation. Net synthesis or degradation of glycogen in the fetus is controlled by the functional balance between glycogen synthase and glycogen phosphorylase. The total content of these two enzymes is relatively constant over gestation. Fetal hyperglycemia increases fetal glycogen deposition by activating glycogen synthase via insulin. Hypoglycemia, glucagon, and cyclic adenosine monophosphate (cAMP) can induce the fetal liver to release glucose by activation of phosphorylase. The glycogenolytic action of glucagon is suppressed by insulin.

Preterm infants have an abbreviated or no third trimester and thus have limited glycogen stores. Fetuses that are growth-restricted on the basis of limited metabolic fuel availability and uteroplacental insufficiency will use these fuels for growth and not for glycogen synthesis.

Gluconeogenesis

Hepatic GNG is completely absent *in utero* and appears in the immediate newborn period.[10] The fetus also has all the four key hepatic enzymes involved in GNG, although their levels are lower than those in adults especially phosphoenolpyruvate carboxykinase (PEPCK), which, at least in the rat, is not expressed *in utero* and appears immediately after birth. GNG can be induced *in utero* by maternal starvation, prolonged hyperglycemia in mother and by cAMP infusion in the fetus. At birth, thyroid, cortisol, and catecholamines stimulate GNG. GNG may be impaired in preterm infants and intra uterine growth restricted (IUGR) infants due to lower PEPCK activity and reduced gluconeogenetic precursors.

Lipid Metabolism

The land mammal with the highest fat content is the human fetus. It increases from 0.5% of body weight in early gestation to 3.5% by 28 weeks to 16-18% by term.[11] During early gestation, embryonic and fetal lipids are derived from maternal free fatty acids (FFA), whereas in advanced gestation there is a gradual shift to *de novo* synthesis in fetal tissue.

Free fatty acids

Placental transfer of triglycerides is null. Essential fatty acids such as ω-6 linoleic and ω-3 α linolenic acids derived from maternal diet are made available to the fetus by the action of the lipoprotein receptors and lipase activities in the placenta. Fatty acid binding protein on placental membrane (FABP pm) preferentially takes up long chain polyunsaturated fatty acids (LC-PUFAs) in the favored sequence of docosahexaenoic (DHA) > α-linolenic > linoleic > oleic > arachidonic acid (ARA).[12,13] Intrauterine requirements ω-6 and ω-3 fatty acids in the human fetus during the last trimester of fetal development through the early weeks of life have been

estimated to be 400 and 50 mg/kg/day, respectively. Though the fetus has a significant capacity for production of DHA and ARA from ω-3 α linolenic and ω-6 linoleic acids, respectively, is this enough throughout gestation?[14] It is suggested that maternal supplementation with DHA may improve neurodevelopmental outcome in offspring.[15]

Lipogenesis is very active in the fetus through the fatty acid synthetase pathway. The high insulin to glucagon ratio in the fetus promotes lipogenesis. The increased maternal nutrition in late gestation uniquely enhances brown fat development and the content of uncoupling protein-1 (UCP-1). These stores are vital postdelivery and UCP-1 allows for rapid lipid mobilization and energy production after birth.[16]

Glycerol

Maternal glycerol is preferentially used for glucose synthesis, saving other gluconeogenic substrates, like amino acids, for fetal growth.

Ketone bodies

Though ketogenesis is not active in the fetus, maternal ketone bodies are readily transferred transplacentally and the fetus can use them as fuel and as lipogenic substrates during maternal starvation, caloric restriction, high fat diet, or diabetes.[17] The fasting and fed states during pregnancy are depicted in Figure 4. Prolonged ketonemia may have neurological implications to the fetus.

Protein Metabolism

Protein is the essential building block. Accumulation of protein results in most of the increase in fetal weight till about 26 weeks gestation. However, no protein is transported across the placenta. Amino acids are actively transported to the fetus by Na^+/K^+-ATPase and H^+ dependent transporter proteins resulting in higher fetal concentrations of amino acids (fetal-maternal plasma concentration ratios 1-5). Protein molecules as small as albumin and as large as gamma globulin pass from maternal to fetal plasma by pinocytosis.[8]

In utero accretion of proteins is highest during the third trimester of pregnancy at 3.6-4.8 g/kg/day. Matching this in the extreme preterm infant postnatally for optimal growth is indeed a very difficult task! In addition to the 10 essential amino acids, fetus needs cysteine, histidine, and taurine. The placenta also produces ammonia that is used by the fetal liver for additional protein synthesis. Some critical amino acids are not transferred across the placenta, but are produced in the placenta. This may be a safety feature as some amino acids like glutamate and aspartate are toxic, so the placenta can produce only the amounts that are needed by the fetus.

These amino acids are used for oxidation, protein, glycogen and fat accretion, and for growth. The amino acids

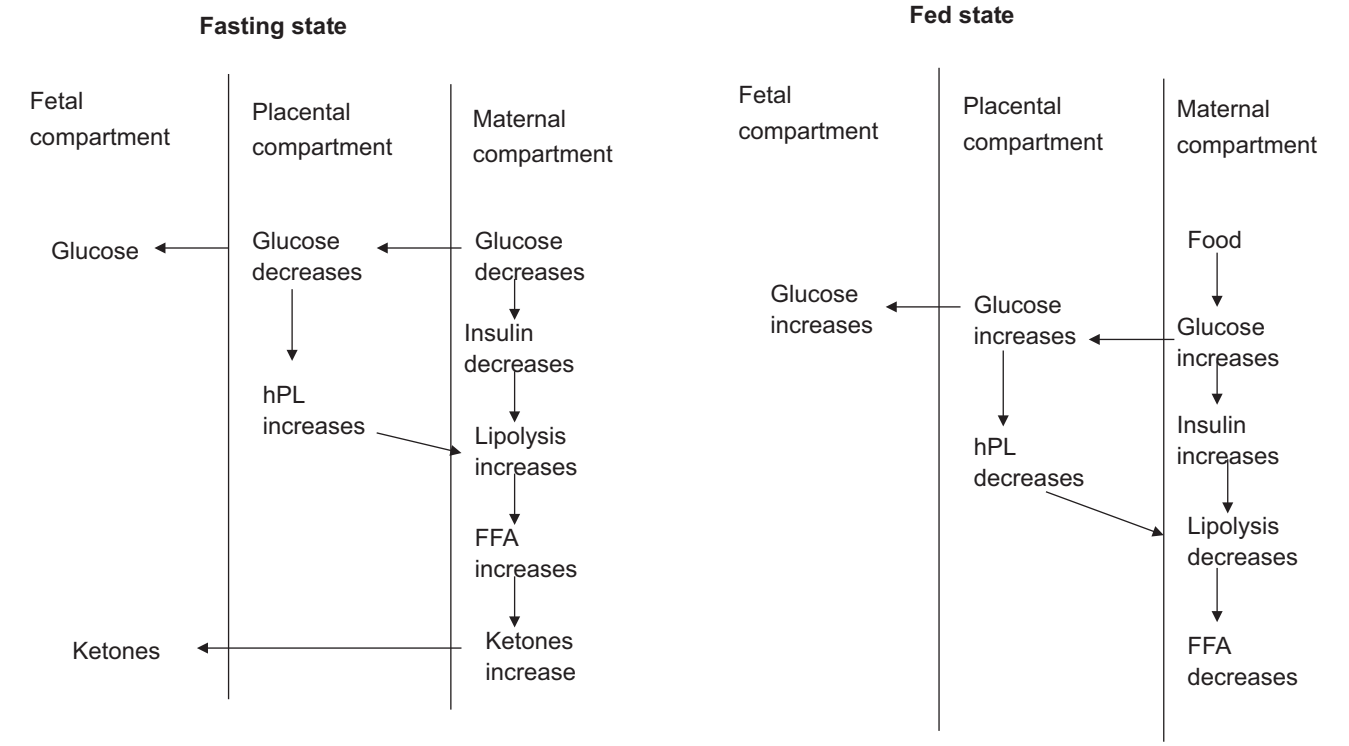

Figure 4: Fasting and fed states in pregnancy (adapted from Ref 8)

contributes significantly as fuel in the fetus as evidenced by:[18]

1. Excess uptake of amino acids relative to rate of deposition in fetal protein
2. High rate of fetal urea production
3. Direct measurement of labeled CO_2 production and excretion during fetal infusions with carbon labeled stable isotope amino acids.

Fetal protein synthesis is dependent on both amino acid and energy supplies. During positive energy balance, glucose utilization as fuel substitutes for amino acids. Insulin promotes nitrogen accretion. During maternal hypoaminoacidemia, as long as the fetal glucose supply is normal, growth is not affected. Conversely during maternal fasting, increased proteolysis occurs but protein synthesis is normal. It is only on prolonged energy and protein restriction, that protein synthesis is reduced to a great extent.[19,20]

In this reciprocal manner, glucose supply and amino acid metabolism are closely balanced and protein accretion and growth are variables that less vital than fetal oxidative metabolism. Thus the fetus develops mechanisms that tend to keep its energy metabolism relatively constant, while growth is, at times of deficient energy supply, expendable.[5]

Maternal Metabolism

The effect of pregnancy on maternal metabolism can be studied in two time frames:

Anabolic first half of gestation

The increased caloric intake sustains fetal growth and facilitates maternal fat deposition under normal insulin secretion.

Catabolic second half of gestation

In this period of exponential fetal growth, with the continuous transfer of glucose and nutrients to the fetus, the fasting maternal glucose and amino acids are lower. Maternal fat stores are mobilized and the resulting hypertriglyceridemia or 'floating fuel' is beneficial to both mother and baby. Increasing insulin resistance (20-60%) is integral to this phase, resulting in three times the pregravid insulin levels (diabetogenic state). Increasing human placental lactogen, progesterone, and estrogen are partly responsible for the insulin resistance. This can unmask a tendency toward diabetes mellitus. These changes are seen when the conceptus rapidly increases in mass from 20 to 24 weeks of pregnancy. The maternal metabolic processes and the underlying hormonal changes are shown in Table 2. The 'accelerated starvation' of the mother guarantees fuel to the fetus at the mother's expense.

Endocrine Regulation of Fetal Metabolism

Hormonal regulation of metabolic substrate utilization and anabolism in the fetus is secondary to the supply of nutrient substrates.

Insulin

Insulin appears in the fetal circulation as early as 10-12 weeks gestational age. Fetal glucose metabolism is relatively independent of the insulin–glucagon regulatory mechanisms. Insulin is more important for enhancing growth than for regulating metabolic fuels during fetal life. Insulin stimulates the growth of specific tissues (e.g., adipose, hepatic, connective, skeletal, and cardiac muscle).

A glucose load elicits a very sluggish fetal insulin response in the nondiabetic mother [Figure 5]. With chronic hyperglycemia, insulin is reduced.[5,21] But in contrast, the fetus of a diabetic mother with pulsatile hyperglycemia responds with a brisk insulin release.[22] Excessive insulin secretion during fetal life resulting from such conditions as maternal diabetes causes the disproportionate growth of insulin-sensitive tissues, resulting in macrosomia. The anabolic effect of insulin is enhanced by a separate direct effect of insulin on mitogen activated protein kinase (MAPK). Lack of insulin, as in infants with transient neonatal diabetes mellitus, always is accompanied by fetal growth restriction. Chronic maternal malnutrition depresses insulin and stimulates release of fetal glucagon.

Insulin like growth factors- IGF-1 and IGF-II

IGFs from the liver have autocrine, paracrine, and endocrine

Table 2: Maternal metabolic processes and hormonal changes

Hormonal change	Effect	Metabolic change
Increased human placental lactogen (hPL)	Diabetogenic Increased glucose tolerance	Facilitated anabolism during feeding Accelerated
Increased prolactin	Insulin resistance	starvation during fasting
Increased bound and free cortisol	Decreased hepatic glycogen stores	Ensures glucose and amino acids to fetus
	Increased hepatic glucose production	
Increased estrogen progesterone and	Increased fat synthesis Fat cell	Anabolic fat storage during early pregnancy
insulin during early pregnancy	hypertrophy Inhibition of lipolysis	
Increased hPL in late pregnancy	Lipolysis	Catabolic fat mobilization in late pregnancy

(modified from Ref[8])

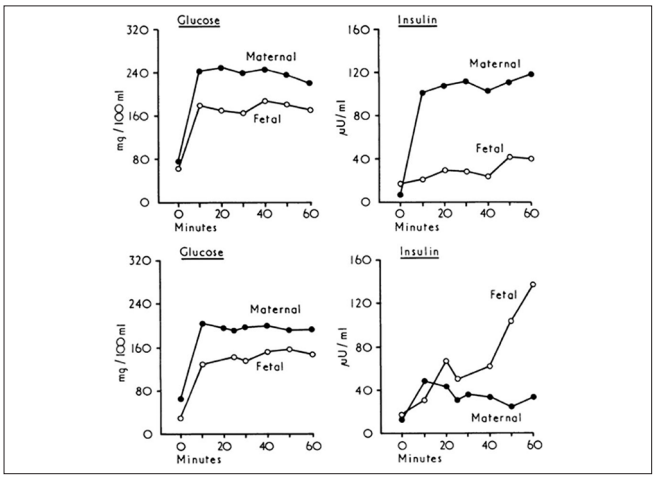

Figure 5: Effect of maternal hyperglycaemia on the fetus in normal and diabetic pregnancies (adapted from Ref 7) A Normal pregnancy, B Diabetic pregnancy

functions. Both IGF-I and IGF-II increase with gestational age. In early gestation, IGF-II is predominant and in later gestation, IGF-I, regulated by nutrient availability promotes growth with insulin and glucose. IGF-I is more responsive to insulin, thyroxine, and glucocorticoids than IGF II. Further, the effect of IGFs on fetal growth is amplified or attenuated by the IGF binding proteins (IGFBPs), which are regulated by nutritional and endocrine signals. In growth restricted fetuses, IGF-I is low.[23] Disruption of the IGF I, IGF II, or IGF I receptor gene retards fetal growth. Silver–Russel syndrome characterized by IUGR, poor postnatal growth, relative microcephaly, triangular face, and feeding difficulties is associated with low levels of IGF II due to hypomethylation defects and maternal uni-parental disomy.

Growth hormone

Growth hormone is abundant in fetal life. It has been suggested as a stimulator of fetal hepatic glycogen synthesis. It may affect insulin/glucose metabolism in a way similar to its postnatal diabetogenic action. However, its action on fetal skeletal growth is negligible due to less receptors. The phenotype resulting from GH deficiency is unremarkable except for micropenis, hypoglycemia, and perhaps a small reduction in birth length.

Glucagon

Glucagon is abundant in fetal life. The number of fetal hepatic glucagon receptors is decreased and insulin receptors higher. This promotes insulin mediated anabolism and decrease glucagon induced catabolism. Critical glucagon/insulin ratio is important for inducing gluconeogenic enzymes. A balance between these two hormones controls gluconeogenic enzyme induction during perinatal life. Cord clamping triggers an increase in glucagon secretion and insulin secretion slowly decreases. This is the trigger for glycogenolysis and gluconeogenesis in the immediate postnatal period.

Adrenergic hormones

During labor adrenergic mechanisms can stimulate hepatic glycogenolysis.

Leptin

Fetal leptin, an adipostatic hormone appears by 90 days gestation, increases after 32-34 weeks and closely reflects the increase in size and number of adipocytes. It is important for fetal growth and may act by modulating growth hormone. It decreases rapidly after birth and may help limit energy expenditure and conserve nutrients for growth. Concentrations of leptin are three times higher in large for gestation (LGA) infants and 12 times higher in small for gestation (SGA) infants. Leptin expression is influenced by other hormones, that is, insulin, thyroid hormones, cortisol but its exact role in fetal and neonatal homeostasis is not understood.[24–26]

Transition to Extra Uterine Life

The neonate must become independent after birth,[27] transitioning from a continuous intravenous supply of predominantly glucose as fuel to a variable and intermittent exogenous intake orally that is the hallmark of the neonatal period. This successful adaptation requires not only an immediate catabolic cascade but also adaptation to enteral feeding. The catabolic cascade includes endocrine stress response, surge in glucagon, low insulin, and glucagon ratio. This mobilizes hepatic glycogen and initiates gluconeogenesis, lipolysis, fatty acid β-oxidation with generation of ketone bodies, and proteolysis that generates lactate and other substrates for gluconeogenesis. Ketone bodies and lactate serve as alternative fuels with glucose-sparing effects, and are especially important in maintaining cerebral energy. The neonatal glucose homeostasis is also consistent with the ontogeny of the glucose transporters. After birth, GLUT-3 in the brain and GLUT-4 in the muscle increase.[4,28] The metabolic transition is summarized in Table 3. Lipolytic activity becomes active after delivery especially as the human milk has a high fat content. The fetus and neonate have a high lipoprotein lipase activity in the liver in contrast to the adult. Fifty percent of the caloric intake of the newborn is from lipids.

Implications for the Clinician

Understanding maternal–placental–fetal metabolism is critical for the management of frequent disorders such as diabetes in pregnancy, IUGR, preterm, and maladaptations at birth.

Table 3: Metabolic transition at birth

Metabolic function	Fetus	Newborn
Source of nutrients	Mother	Endogenous
Endogenous glucose production	Minimal	Highly active
Lipolysis/Ketogenesis	Minimal	Highly active
State	Anabolic	Catabolic
Hormone concentration		
Insulin	Low	Low
Glucagon	Low	High
Epinephrine	Low	High
Hormone receptor		
Insulin density	High	Decrease
Insulin affinity	High	Decrease
Glucagon density	Low	Rapid increase
Liver enzyme		
Phosphorylase	Low	High
PEPCK	Low	High

Hypoglycemia

Blood glucose concentration falls rapidly after birth, reaching a nadir by 1 h of age and then rising to stabilize by 3 h of age. Small energy stores, delayed maturation of gluconeogenesis, hyperinsulinemia, or increased demands, may hamper the normal metabolic transition and lead to hypoglycemia. Under these conditions, the most vital organ, the brain, tries to maintain the metabolism by increasing blood supply and glucose transfer to brain, using alternate fuels such as lactate, fatty acids, ketone bodies.[29] Monitoring of at risk infants, prevention, and early treatment of hypoglycemia are critical to prevent adverse neurodevelopmental outcome.

Extreme preterm neonate

Neonatal intensive care units now routinely take care of 24-28 weeks. The glucose homeostasis in extreme preterm neonates is precarious. On one hand, they are at risk for hypoglycemia and need glucose infusion right from birth. But they are also unable to completely suppress endogenous glucose production even with high glucose infusions. This hepatic unresponsiveness combined with diminished pancreatic β cell response predisposes the extreme premature infant to hyperglycemia.[4] The range of euglycemia of 50-145 mg/dl may represent a more acceptable range for term and preterm neonates, except in micropremies. Providing adequate proteins and calories to match intrauterine accretion is also a big challenge in these infants.

Maternal Diabetes

Pederson's hypothesis

Increased fetal glucose supply from the placenta increases fetal insulin secretion,[30] which augments fetal glucose and lactate accretion. The hyperinsulinemia promotes lipogenesis and macrosomia. Rather than chronic hyperglycemia, it is pulsatile hyperglycemia that results in glucose stimulated insulin secretion (GSIS). Despite normal HbA_{1C}, infant of diabetic mothers may be macrosomic due to poorly controlled postprandial sugars. A more severe acute hyperglycemia can initiate such profound metabolic changes to result in fetal acidosis and death. Close monitoring of maternal blood sugars is therefore vital to prevent neonatal complications in infant of diabetic mothers.

Intra Uterine Growth Restricted

Impaired placental growth and function resulting in decreased energy substrate rather than dysregulated fetal endocrine responses is the primary defect in IUGR.[31] Lower lipolysis in the mother has been shown to reduce substrate availability in IUGR.[32] The PGT capacity is reduced due to a small placenta and reduction in glucose transporters. Owens, *et al*.[33] demonstrated impaired glucose stimulated insulin secretion in sheep fetus with impaired placental function. IUGR fetuses are not able to produce adequate amount of insulin due to reduced β islet number and size, by lengthening G1, S, and G2 stages of interphase and decreasing mitosis near term. Limesand, *et al*.[22] demonstrated that plasma insulin concentrations in the IUGR fetuses are 64% lower at baseline and 77% lower after GSIS. The IUGR fetus copes in two ways:[5,34]

1. Upregulation of mechanisms regulating glucose utilization
   a. Glycogenolysis
   b. Gluconeogenesis
   c. Use of alternate fuels
   d. Increase in GLUT 1 in placenta and GLUT 4 in skeletal muscles
2. Downregulation of mechanisms regulating growth

One question that needs to be answered urgently is—Can we intervene to prevent growth restriction *in utero* and thereby alter the potential metabolic problem?

Fetal Origin of Adult Disease

Fetal over nutrition and under nutrition have been implicated in the genesis of the metabolic syndrome and is the deep focus of preventive medicine. Macrosomic infants of diabetic mothers may exhaust their insulin reserves in the face of hyperglycemia secondary to obesity and insulin resistance.[5]

IUGR infants probably have a low β cell mass and this coupled with the added insulin resistance of obesity later in life leads to the metabolic syndrome (the thrifty phenotype hypothesis). For each 1-inch decrease in abdominal circumference at birth, serum cholesterol and LDL-C concentrations in older adults are increased by approximately 10 mg/dl.[35] A meta-analysis including 147,000 persons has

shown inverse relation between birth weight and subsequent development of ischemic heart disease, with a 10-20% lower risk observed per kilogram higher birth weight.[36]

Fetal hypoglycemia in the absence of impaired fetal growth has also been found to be associated with lower insulin secretion.[37,38] Obesity-induced insulin resistance, altered expression of GLUT 4, defective oxidative phosphorylation, genetic mutations, and increased adrenocorticomedullary activity have all been evaluated in the pathophysiology of fetal origin of adult diseases.

Conclusions

The human fetus is capable of controlling and partitioning energy to some extent through many complex, dynamic processes. Glucose is the primary fuel for fetal metabolism. However, the fetus is capable of utilizing lactate, amino acids, ketone bodies and others too. Continuous supply of fetal nutrients rather than hormones control fuel homeostasis. Oversupply of undersupply of nutrients can permanently program the fetal metabolism adversely.

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