Abstract
Optimal fetal growth resulting in a ‘normally grown’ term infant is of paramount importance for assuring a healthy start for postnatal growth and development. Fetal, infant and childhood growth restriction is an important clinical problem for obstetricians, neonatologists, pediatricians and globally, for public health. Worldwide, an estimated 20 million infants are born with low birthweight and a substantial proportion are small for gestational age. Many advances have been made in defining growth restriction by prenatal techniques, thus allowing the recognition of intrauterine growth restriction. Distinguishing infants who are small but have appropriate growth potential from those with growth restriction is important in order to apply obstetric surveillance, anticipate neonatal problems and plan for postneonatal guidance. It is clear that the fetus in growth-restricted pregnancies has limited supply of nutrients and oxygen. The resultant changes, if involving the placenta as well, can lead to circulatory and metabolic changes affecting both short- and long-term survival and development. In this paper, the causes and immediate consequence of being born with low birthweight, intrauterine growth restriction or small for gestational age will be discussed.

Under optimal circumstances, fetal growth occurs in sequential patterns of growth (tissue and organ) and maturation. Uteroplacental function, maternal environment and genetic factors play a role in modulating this growth [1–4]. Alteration in any of these factors may become rate limiting resulting in altered growth resulting in intrauterine growth restriction (IUGR). A clear distinction needs to be made between IUGR which may affect survival in utero, alter ad-
aptations to labor and delivery stressors as well as neonatal transition and small-for-gestational-age (SGA) and low-birthweight (LBW) infants. IUGR indicates a reduction in the expected growth trajectory in utero and is traditionally based on fetal weight; fetal growth at term may be predicted based on ultrasonographic findings in the second trimester, and growth curves are available based on maternal weight and height, parity, ethnicity and fetal gender. SGA denotes an infant whose weight is lower than $-2$ or $-3$ standard deviations from population norms. It is important to remember that an accurate estimate of gestation age and definition of SGA is essential for postnatal care since it is associated with significant antenatal and postnatal pathology. SGA also includes constitutional smallness which does not carry the same risks as true pathological SGA. SGA often represents placental dysfunction and may be associated with preeclampsia, preterm labor, placental abruption, intrapartum complications and fetal mortality [5]. Birthweight, in both developing and developed countries, is considered the single most important factor affecting neonatal and postneonatal mortality [6]. LBW is defined by the WHO as a birthweight <2,500 g; however, plots of cumulative frequency distribution of birthweight show two different normal distributions, and 2,000 g as a lower cutoff point has been suggested [7]. Nonetheless, LBW is caused by either premature birth or IUGR or both. The various growth curves used to define appropriateness of growth for gestational age, fetal metabolism and maternal metabolic adjustments during pregnancy are beyond the scope of this paper and are discussed elsewhere in this monograph.

It is however important to briefly mention the long-term consequences of reduced birthweight. LBW in the fetus has been associated with adult-onset hypertension, type II diabetes, obesity and cardiovascular disease. These consequences occur in infants born small and exhibit increased growth including catch-up growth. The fetal origin hypothesis states that poor nutritional status in the mother produces reduced birthweight and results in ‘reprogramming’ that results in adult-onset diseases. The risk for the adult diseases is not universal and may be two to three times that of a normal population. It is also recognized that twins (who may not have placental dysfunction causing reduced body size) do not have a higher incidence of adult diseases compared with other adults. Increased weight gain in infancy and childhood either as part of catch-up growth or excessive growth is becoming an established risk for the development of metabolic syndrome although this entity is not well defined in children. The increased growth is primarily central fat and not lean body mass; this altered growth is associated with insulin resistance. Alternative hypotheses have been put forth where genetic factors or poor intrauterine nutrition could result in insulin resistance and make the individual susceptible to diabetes and heart disease.
Immediate Metabolic Consequences of IUGR and LBW

Risk factors for LBW are summarized in Table 1. It should be emphasized that many of the listed factors are common for both IUGR and prematurity.

Table 1. Factors associated with growth restriction

<table>
<thead>
<tr>
<th>Classification</th>
<th>Factors</th>
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</thead>
<tbody>
<tr>
<td>Demography</td>
<td>Black, Lower socioeconomic status</td>
</tr>
<tr>
<td>Prenatal factors</td>
<td>Short stature, Poor nutritional intake, Chronic disease, Transgenerational (low birthweight of mother)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Multiple gestation, Placental dysfunction (chronic diseases affecting delivery of nutrients), Altitude, Infections, Fetal factors (genetic, renal agenesis etc.)</td>
</tr>
<tr>
<td>Other</td>
<td>Habitual smoking, Alcohol and illicit drug use, Short interpregnancy interval</td>
</tr>
</tbody>
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Modified from Committee to Study the Prevention of Low Birthweight, Institute of Medicine [25].

On the other hand, nutritional status of women in both developing and developed countries could lead to insulin resistance or obesity [9].

Scope of the Problem

Worldwide, more than 20 million infants are born with a birthweight <2,500 g, and of these, it is estimated that 30–40% are SGA at term gestation. SGA status at lower gestational ages is not known on a population level, although it is known that a great majority of extreme premature infants who survive are born SGA. Population means and SD may be misleading since there may be less variability within a family with respect to birthweight rather than a population. Accurate assessment requires proper definition of growth and hence, weight, and that depends on the following: accurate dating of a pregnancy; use of appropriate growth standards, and growth and weight standards need to be free of confounding factors that affect them, for example, smoking, diabetes, etc. Fetal growth restriction originates early in gestation in approximately 20% of the infants, and these infants are usually growth restricted in a symmetric fashion: weight, length and head circumference are all affected. Late-onset growth restriction occurs due to uteroplacental insuf-
ficiency and, therefore, limited transfer of nutrients and oxygen, during the last trimester of pregnancy. The resultant growth restriction generally spares the head to the greatest extent and the length to a more limited extent (table 2).

**Anticipated Problems and Management Prior to Delivery**

There are numerous studies demonstrating reduced umbilical blood flow in growth-restricted fetuses and that the reduction can occur quite early in gestation. In addition, umbilical blood flow closely approximates the growth of the fetus and decreases slightly if expressed per kg as gestation progresses in normal pregnancies [10]. The ductal shunt (ductus venosus) is however increased in growth-restricted fetuses. Thus, an increase in ductal shunt combined with a decrease in umbilical flow in growth-restricted fetuses can result in hepatic injury unrelated to infection in growth-restricted neonates [11, 12]. Maternal undernutrition and an increase in ductal shunting have also been reported [13].

Management principles for the care of a pregnancy with a suspected growth-restricted fetus are as follows:

- Appropriate maternal and fetal care and close monitoring of the fetus
- Limit maternal activity
- Improve fetal oxygenation by providing oxygen to the mother if needed
- Assessment of fetal well-being
- Coordinate delivery with the neonatal team

**After Birth**

A neonate who is SGA may develop several neonatal problems. If marginal placental perfusion is suspected, uterine contractions and prolonged labor may compromise fetal gas exchange. Myocardium of the fetus may have diminished
glycogen stores and less so if premature also, and these fetuses may not withstand asphyxia. Meconium passage in utero may also occur due to fetal hypoxia and stress. The infant may exhibit physical features of the disease process that resulted in IUGR/SGA/LBW. Among SGA infants with perinatal stress, up to 10% continue to have hypoglycemia beyond the first week of life [14]. This hyperinsulinism is responsive to diazoxide, and exact pathogenic mechanisms are not clear.

The perinatal mortality of IUGR infants is 10–20 times higher than that of a normal-weight infant. As alluded to previously, these infants are at high risk for perinatal asphyxia and its sequelae including multiorgan dysfunction and failure. Concomitant with these, there may be metabolic problems including hypoglycemia. Physiologically normal appropriate-for-gestational-age infants are susceptible to the development of hypoglycemia if feedings are delayed in the first few hours of life. The susceptibility to transient hypoglycemia is associated with developmental lags for both hepatic ketogenesis and gluconeogenesis and is aggravated in infants with limited glycogen stores [15]. A delay in PEP-CK, carnitine palmitoyl-transferase 1 and β-hydroxy-β-methylglutaryl-coenzyme A synthase has been described in the guinea pig and the rat, suggesting these changes as a cause of the hypoglycemia [16]. SGA infants have also demonstrated similar mechanisms for the development of hypoglycemia, low glycogen stores, delayed oxidation of FFA and induction of PEP-CK [17, 18]. Hypocalcemia may occur due to excess phosphate release from damaged cells or acidosis, but is not a consistent feature of SGA per se unless accompanied by prematurity.

Fasting hypoglycemia is very common, and the incidence is greatest during the first 3 days of life, largely due to reduced hepatic glycogen content [19]. Glycogenolysis is limited due to lack of glycogen stores, and glucose production occurs from incorporation of lactate and specific amino acid precursors into glucose. Hypoglycemic SGA infants have elevated alanine and lactate levels, and have been demonstrated to have an inability to raise blood glucose levels after alanine administration [20]. Immediately after birth, hypoglycemic SGA infants may also exhibit lower plasma FFAs and fasting glucose levels correlate with FFA and ketone body levels. In addition, as parenteral nutrition is established, intolerance to intravenous lipids is evidenced by raised triglyceride concentrations in plasma. However, ketone body formation is attenuated, suggesting that oxidation of FFA and triglycerides are limited in SGA infants. The latter, deficient oxidation of fatty acids may be responsible, in part, for the fasting hypoglycemia observed in these infants [21]. Hypoglycemia may also be due to hyperinsulinemia or excessive sensitivity to insulin in infants who are SGA. In addition, glucagon fails to enhance blood glucose levels suggesting...
an abnormality in counter-regulatory mechanisms. Provision of glucose infusions at 4–8 mg/kg per min generally alleviates hypoglycemia.

Temperature Regulation

Temperature regulation becomes an important clinical issue in infants who are born after uteroplacental insufficiency since these infants may manifest hyperthermia because of failure of heat-eliminating mechanisms. On exposure to the usually cold environment in the delivery room, SGA infants increase heat production; however, with continued exposure to a cold environment, core temperature decreases since heat production is less than heat loss. Initially, brown adipose tissue which is not necessarily lost in IUGR fetuses accounts for the increase in heat production. Infants who are SGA have a narrower neutral thermal environment than term or preterm infants and should be managed accordingly. Both hypoglycemia and hypoxia interfere with heat production and contribute to thermal instability. Thus, maintenance of appropriate body temperature is an important clinical issue since postnatal weight gain would be affected by continued hypothermia.

The Metabolic Changes

The metabolic changes with respect to respiratory quotient that occurs in SGA infants are similar to those observed in AGA infants. These infants demonstrate a shift towards free fatty oxidation and a lower respiratory quotient. Basal oxygen consumption may be decreased similar to that observed in IUGR infants in utero suggesting a decrease in oxidizable substrate. Once substrates are provided in the form of exogenous nutrition, an increase in oxygen consumption is observed. In addition, SGA infants do not demonstrate the usual 10–15% weight loss as observed in premature infants. In two studies with a small number of infants (n = 7 and 5), SGA infants <35 weeks’ gestation were noted to have a maximal weight loss of 2–5% [22, 23]. Moreover, infants in the second study were reported to have regained their birthweight dissimilar to AGA infants. The resumption of adequate energy intakes in these SGA infants is accompanied by an increase in oxygen consumption and may represent energy cost of growth. One of the nutritional factors generally not considered clinically is that SGA infants demonstrate increased fecal fat excretion, less energy storage and protein loss. There are SGA infants, however, who do not demonstrate these increases and demonstrate lower rates of weight gain. It is possible that this lack of weight loss and subsequent weight gain may have implications for the observed adult-onset diseases seen in SGA infants.
Blood Volumes

Blood volumes vary with methodology (plasma vs. red cell labels), time of cord clamping and may vary with delivery complications. There are no significant differences between term and preterm neonates with regard to blood volumes. IUGR does not appear to affect blood volume or red blood cell mass. However, in SGA infants with polycythemia, blood volume is increased (108 ml/kg vs. 86 ml/kg) compared to AGA infants [24]. Implications of the polycythemia-hyperviscosity syndrome as a result of fetal hypoxia (increased erythropoietin synthesis) or a placental-fetal transfusion include hypoglycemia and hypoxia, hyperbilirubinemia and associated risks with increased red cell mass.

To summarize, the neonatal effects include hypoglycemia, hypocalcemia, hypothermia, perinatal depression/asphyxia, meconium passage in utero (therefore, higher risk for meconium aspiration syndrome), and polycythemia.

Prognosis is obviously dependent on the etiology, duration of the effects causing SGA/IUGR, and includes increased mortality compared to appropriate-for-gestational-age infants, increased risk for perinatal complications, increased risk for neurological dysfunction, increased risk for adult-onset hypertension, glucose intolerance, obesity and long-term growth problems depending on cause.

Disclosure Statement

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References


