Abstract
The need to prevent low birthweight (LBW) defined as a birthweight ≤2,500 g is presently well recognized, not only because of the immediate consequences increasing the risk of neonatal death and burden of disease but also in terms of the impact of being LBW on lifelong health and well-being. Children are born LBW (<2,500 g) either because they were born too early (true preterm LBW infants) or alternatively they failed to grow adequately despite a normal duration of gestation (intrauterine growth retardation IUGR). In this later case, the weight may be over 2,500 g, but the infant is lighter than expected for his/her gestational age. In fact, many preterm infants are to some degree growth retarded. Despite the differences in origin, all LBW categories are considered at increased risk of neonatal death and later morbidity.

Preventive actions are more likely to succeed if we consider the nutritional interventions as part of a package that addresses in a holistic manner the full spectrum of needs of women from before conception as well as during pregnancy. We have gained sufficient experience with single nutrient and/or ‘magic bullet’ approaches to learn from this and avoid them in the future. New fetal growth standards (INTERGROWTH 2012) represent major progress in terms of evaluating the effect of early life events on later growth, health and well-being. Thus, for the first time, clinicians and researchers will have sequential longitudinal data that will serve to characterize whole body as well as brain, liver, and long bone growth, relating this indirectly to placental blood flow and transfer function, neonatal health, morbidity and mortality.
**Introduction**

The need to prevent low birthweight (LBW) defined as birthweight ≤2,500 g is presently well recognized, not only because of the immediate consequences increasing the risk of neonatal death and burden of disease but also in terms of the impact of being LBW on lifelong health and well-being. Children are born LBW (<2,500 g) either because they were born too early (true preterm LBW infants) or alternatively they failed to grow adequately despite the duration of gestation (intrauterine growth retardation, IUGR). In this later case, the weight may be over 2,500 g, but the infant is lighter than expected for his/her gestational age. So, we may have LBW due to preterm birth or IUGR; in addition, most preterm infants are to some degree growth retarded [1]. Despite the potential differences determined by the suggested groupings, all LBW categories are considered at increased risk of neonatal death and later morbidity. In addition, among the LBW, there might be true IUGR and constitutional small for gestational age (SGA; i.e. children that are small but are growing according to all their potential) [2].

The relative contribution of each of these conditions to the prevalence of LBW will differ by country depending on prevalence of infections, undernutrition, sanitary conditions, access and quality of the health care system among several factors [3]. In order to dissect the contribution of maternal nutrition to the burden of LBW, there is a need to define as accurately as possible the relative contribution of each of these conditions to the problem [4]. Defining effective preventive strategies requires that we have the best possible estimates of how these factors operate in isolation and in synergy with each other. Ideally, LBW prevention should be cause specific in order to enhance the opportunity for effective action (see fig. 1). The implications of this model to LBW prevention – the topic of this paper – are multiple. Firstly, it may serve to guide what is the most effective single intervention based on the estimated population-specific attributable risk or what are the best combined interventions in a given setting considering the additive or synergistic interactions between the selected actions [5]. Unfortunately, few nutritional intervention studies have been designed with a broad conceptual model in mind; in most cases, single nutrient interventions are defined by the priorities established by the funding agency or the investigator’s interest. The model may also serve to explain why in most cases effective actions to prevent LBW require that we affect multiple factors amongst which nutrition is only one of them. It may also serve to explain why a given intervention may be very successful in one setting while in others show moderate or null impact. Preventive actions are more likely to succeed if we consider the nutritional interventions as part of a package that addresses in a holistic manner the full spectrum of needs of women from before conception as well as during pregnancy. We have gained sufficient experi-
ence with single nutrient and/or ‘magic bullets’ approaches to learn from this and avoid them in the future. We must examine the causal web for LBW in a context-specific manner before we define what we need to do to prevent it; there are clearly no solutions that we can think of that will work under all conditions. Unfortunately, establishing the relative contribution of each primary factor and underlying conditions causing LBW is very difficult, particularly in poor countries where this differentiation is most critical, given the high prevalence of LBW [6].

In most of developing countries, even something as basic as establishing the timing of conception is a difficult task, early ultrasound is rarely available except in the larger cities, and even there it will be available only to those that can afford it. Even if it were available, it might not be used early enough, since most women seek medical care well advanced into the pregnancy. An alternative would be to use an indirect measurement of gestational age such as date of last menstrual
period; however, in most places the first visit might be at a late stage in pregnancy when most of women do not recall this date. Even if we are able to establish that the fetus is a true IUGR rather than a constitutional SGA, we might not be able to really confirm this diagnosis (fig. 2) since the predictive models based on clinical information perform rather poorly and the variables considered are not readily available in a developing country setting [7].

[Fig. 2] Categorization of growth according to duration of gestation (weeks) and fetal nutrient balance assessed by bodyweight in grams. LBW is defined by a birthweight <2,500 g, term gestation is defined by being born at >37 weeks' gestation. IUGR can affect preterm or term infants.

[Fig. 3] Critical timing is the time in the human development cycle where nutrient deficiencies or excess have significant impact on long-term health. The critical period for some nutrients such as folic acid or the need to control high blood sugar is before the time of conception; for other nutrients, the critical time is from early gestation, while for yet another set of nutrients the critical period extends beyond fetal life into infancy. A lack of one or more essential nutrients may affect future growth and development. EFA = Essential fatty acids; AA = amino acids; BMI = body mass index.
Appropriate intrauterine growth is key to ensure survival in the first days of life; adequate liver glycogen stores are vital to prevent hypoglycemia and avoid its consequences. The maturation of intestinal function is of vital importance since appropriate carbohydrate and protein supply is vital to secure early recuperation of the depletion typical of infants born IUGR. The early phase of recovery of IUGR is an important factor in determining later linear growth during infancy and final adult stature. Further evidence suggests that there are transgenerational effects of being born IUGR, thus affecting the growth of the next generations (fig. 4). The IUGR condition has been associated with poor school performance and low adult productivity; thus, optimizing fetal and early postnatal growth becomes a key factor in human capital formation, especially in developing countries. More recently, birthweight has also been associated with a myriad of outcomes that impact adult mortality and morbidity such as cardiovascular disease, some forms of cancer,

**Fig. 4.** Diagram represents the effect of nutrition at various stages of the life course. Effects in early life may affect structure and function with lifelong consequence at virtually every step of the life course. The cycle is closed by the effect of nutrition of mothers from early to adult life on fetal growth, thus affecting the next generation. Modified from UN ACC/SCN Report on Nutrition Challenges for the 21st century, Standing Committee on Nutrition, 2000.
diabetes, obesity and stroke [8, 9]. In fact, these observations support the concept of the early origin of adult diseases hypothesis, recently coined as Developmental Origins of Health and Disease. However, there is great heterogeneity in the prevalence of these later outcomes; not all LBW children will develop diabetes or will have decreased cognitive performance; the short- and long-term outcomes of LBW will be also dependent on the underlying cause leading to LBW.

There is now a better understanding of the mechanisms that link early life events to later health. The proposed hypothesis is that events taking place in the intrauterine period and the first months of life induce epigenetic changes (DNA methylation and/or histone modifications that affect gene expression without changes in DNA sequence) [10, 11]; in some cases, the changes are associated with an advantage to withstand the detrimental conditions that induced them, and thus may have a clear short-term benefit. However, this adaptation may render a disadvantage under environmental conditions in later life. For example, acquiring peripheral insulin resistance may be of relevance to the IUGR fetus in order to support fuel supply for the brain; however, maintaining this condition would be deleterious in later life since it will favor central obesity and increase the risk of diabetes and hypertension [11].

Epigenetic modifications induced by malnutrition or by specific nutritional deficits such as, folate, vitamin B\textsubscript{12} and low-protein diets have been described. These observations suggest that epigenetics may not only provide the biological explanation to link LBW to long-term health, but also it might provide us with the opportunity to test the efficacy of nutritional supplementation to revert the adverse long-term outcomes [12]. The interpretation of the observations leading to Developmental Origins of Health and Disease, particularly in developing countries, may also be confounded by the presence of socioeconomic and other environmental conditions that may impose additional risk for chronic diseases in adult life as well as limiting fetal growth. In fact, these structural causes are probably most important in explaining differences in LBW prevalence between countries; but they do not explain variation within a given population. We recognize the importance of taking the necessary actions to decrease income inequalities and access to food and health by addressing the economic and political structural factors that condition LBW; however, this is not the focus of this paper.

**Genetic Influences on Fetal Growth**

This is perhaps most clearly demonstrated by the consequences of an abnormal number of chromosomes (aneuploidy). Turner’s syndrome (45 X0), trisomy 21, trisomy 13 and 18, triploidy and polyploidy are all associated with poor fetal
growth [13]; experimental studies have shown slow cell division in trisomic or triploid cell lines. Aberrant fetal growth also accompanies non-aneuploid disorders. Hereditary gigantism (Sotos syndrome) and the genetic forms of dwarfism represent extremes. Uniparental disomy (abnormal parent-of-origin genetic expression) of chromosome 7 is associated with poor growth in Silver-Russell syndrome [14–16], while a similar abnormality of chromosome 11 leads to fetal overgrowth in Beckwith-Wiedemann syndrome (BWS) [16, 17]. The effect of the environment on the early development of the embryos transferred after in vitro fertilization (IVF) characteristically incubated under high glucose concentrations offers further insights into this phenomenon; the distribution of birthweights of infants born from IVF is displaced to the right (towards higher birthweights); moreover, there is an increased incidence of BWS in babies born after IVF procedures [18]. In summary, genetic makeup has a profound influence on fetal growth. Multiple genes influence the variability in birthweight observed among different ethnic groups, ranging from a mean birthweight of 2,400 g in pygmies to a mean of 3,500 g or greater in affluent populations of industrialized countries. The effect of the genotype is also evident in the greater birthweight among males, averaging 150 g greater than in females at term.

Uterine Milieu and Placental Influences

Environmental influences on fetal growth include the placental structure and function, uterine and placental blood flow, and local umbilical circulation [19, 20]. Taken together, these flows determine substrate and oxygen flux available to the growing fetus as well as the clearance of excretion products and carbon dioxide [21]. In general, the placenta and baby grow proportionately; large babies have large placentas and small babies, smaller placentas; normally, the placenta weighs about 20% of the baby’s weight. Conditions that compromise placental localization, size and function such as abnormal uterine anatomy, ectopic placental implantation, placental abruption or infarction, placental hemangioma or arteriovenous shunts, congenital infections, and abnormal cord insertion may adversely affect fetal growth [22]. Increased placental vascular resistance measured as high resistance to blood flow at the umbilical artery documented by Doppler ultrasound and imaging has served to document the key role of blood flow, and hence substrate flux, in IUGR associated with tobacco smoking, preeclampsia and/or long-standing hypertension, maternal gestational diabetes with vascular compromise [21, 23]. The placenta also influences fetal growth by secreting placental hormones and growth factors in addition to regulating blood flow; the placental surface area defines maternal-fetal
exchange. The placenta also affects fetal growth indirectly through modification of blood and substrate flow or directly by regulation of cell replication and differentiation [24].

**Maternal Nutrition**

Maternal overall nutrition is critical for fetal growth, although the mother tends to buffer the effect of adverse environmental conditions on the fetus. Both pregestational weight and weight gain during pregnancy are positively correlated with infant birthweight. The classic studies of the Dutch famine during World War II showed a mean birthweight reduction of 300 g among infants whose mothers suffered severe caloric deprivation during the last trimester of gestation [25]. In previously well-nourished mothers, caloric deprivation must be quite extreme before fetal growth is compromised. However, in women from developing countries, where malnutrition is entrenched over generations, a moderate energy deficit may have an adverse effect. In this regard, studies have shown that maternal height, partly the result of early nutritional influences, has a positive association with birthweight [26–29]. After 2 years of age, the growth of the infant correlates better with mean parental height rather than maternal height alone; genetic factors contributed by both parents are important in determining final size while early maternal nutrition, reflected in maternal height, is the major determinant of fetal growth. The effects of maternal size may be multigenerational. Mothers who were SGA at birth are at greater risk of having an SGA or preterm baby [30]. These effects may be mediated through the size of the uterus and its capacity to hypertrophy and increase blood flow in response to pregnancy. First-born infants on average weigh less than subsequent infants. Mothers <15 and >35 years of age have a higher incidence of LBW babies, only partially explained by parity and socioeconomic risk factors. Maternal nutrition, especially in adolescents, and uterine and placental factors are thought to play a role. The practical consequence of these findings is that for research purposes and even in clinical use the evaluation of the adequacy of fetal growth and birthweight should take into consideration infant sex, maternal height and birth order in addition to gestational age. In addition, access to adequate food by women may be limited by social, cultural and/or economic factors; in many societies, women are given lowest priority in access to quality foods and thus are most affected by malnutrition, especially micronutrient deficits. This is often missed in studies of household food security. Unless these factors are considered, we will miss undernutrition in our assessment of the relative importance of maternal malnutrition. Discrimination of women on religious or cultural grounds is
also often a cause of maternal malnutrition; this is particularly the case in low-income countries where young adolescent women are often exploited and have to work under conditions of near slavery.

**Micronutrients**

Micronutrient minerals and vitamins are increasingly recognized as agents that affect embryogenesis and the incidence of congenital malformations. Folate intake before and during early embryogenesis (fig. 3) alters the incidence of neural tube defects [31]. The involvement of a genetic component for neural tube defects is evident in the high rate of recurrence in families and individual mothers. Neural tube defects are also more frequent in certain ethnic groups [32]. If neural tube defects were solely genetic, prevalence should not vary over time, yet neural tube defects are more frequent in periods of nutritional deprivation, such as during the 1944–1945 Dutch Famine [33]. These observations led to the discovery of the striking benefit of maternal administration of doses of 400 μg of folic acid preconceptionally [34]. Folic acid from food sources must be reduced to tetrahydrofolic acid before it is metabolically active. This is genetically determined by the activity of methylenethetrahydrofolate reductase, 35–50% of mothers bearing children with neural tube defects have been found to have low enzymatic activity, thus accounting for the protective effect of folate supplementation [35]. Heterogeneity in receptor-mediated folate transport may explain additional susceptibility to neural tube defects unrelated to reductase activity [36]. Retinoic acid, derived from retinol (vitamin A), is a regulator of gene expression and a teratogen early in embryonic development. Of interest, retinoic acid decreases the risk of spina bifida in animals. The folate receptor gene is a target for retinoic acid transcriptional regulation, providing a possible explanation for folate-retinol interaction. Regulation of folate receptors may explain the occurrence of neural tube defects in association with low vitamin A intake. Maternal zinc deficiency has also been implicated in abnormal fetal growth and enhanced susceptibility to such teratogens as alcohol, valproic acid and arsenic. There have been a number of interventions that provide single or multiple micronutrients to pregnant women with the objective of decreasing LBW. These studies have shown that the direction and magnitude of the results depends on the baseline nutritional status and possibly the genetic background of the population; thus, the specific combination of micronutrients needed should be defined based on the assessment of micronutrient status of the particular population to be intervened. Several participants in this workshop have addressed and discussed in detail specific micronutrient interventions and where the evidence stands regarding their efficacy and effectiveness.
Gene-Nutrient Interactions

The beneficial effect of folic acid is only one example of the relationship between genetic makeup and diet. The interaction of genes and the early diet not only determines brain development, growth and body composition but also the later prevalence of nutrition-related chronic disease and some types of cancers. Genes are differentially expressed depending on the exposure to the epigenetic nutrients and toxicants. Thus, a similar genotype may define multiple phenotypes. Regulation of gene expression can occur at multiple levels. Nutrients can bind to specific or non-specific ligands that interact with response elements in DNA. Nutrients may change the phosphorylation status of a protein and thus its activity. At the posttranscriptional level, nutrients may modify native RNA processing, mRNA transport and stability, and breakdown rates. Nutrients may modify the rate of mRNA translation. Finally, nutrients can modify the turnover rates of enzymes and other proteins, thus affecting their activity level. Pregnancy is undoubtedly one of the periods of life in which genes can be regulated by epigenetic changes. Several studies have already shown how caloric restriction or exposure to particular micronutrients before and during gestation induces lasting epigenetic modification in the offspring; it is thus important to consider the future impact that these changes might have on lifelong health; based on present evidence, it is plausible that they will define the future predisposition or amelioration of risk to develop chronic diseases.

Maternal Medical Disorders

Preeclampsia, chronic hypertension, collagen vascular disease and renal disease all affect fetal growth by compromising maternal nutritional status and interfering with uterine and placental perfusion. Severe maternal anemia and diminished cardiac output secondary to heart disease and/or cyanotic congenital heart disease may affect fetal growth by decreasing oxygen availability to the maternal uterine compartment. Early abnormalities in embryonic fuel metabolism in prediabetic or diabetic mothers may play a role in determining abnormal fetal growth and may also be teratogenic; later in gestation, maternal glucose elevation induces fetal hyperglycemia leading to hyperinsulinism and macrosomia with enhanced growth of peripheral adipose tissue, muscle hypertrophy and increased liver glycogen stores. The goal of preventive health care and nutrition before and during pregnancy must be to avoid both IUGR and macrosomia. Maternal obesity and its associated metabolic complications are increasingly being observed even in low-income population settings worldwide. Pregnancy is itself a state of metabolic stress; thus, the combination of these factors may lead an increased risk
of abnormal fetal growth. This is a very challenging field since ideally preventive actions need to be taken preconceptionally. Only if the latter were not possible should we carefully attempt to control the disease condition during pregnancy in order to avoid disarrangements that might affect the fetus or the pregnancy.

**Intrauterine Infections**

Several maternal infections including rubella and cytomegalovirus infections can impair fetal growth. Toxoplasmosis, syphilis and herpes infections, although less frequent during the first trimester, may affect fetal growth by arresting cell replication during critical stages of development, causing typical patterns of malformations and severely compromised growth. Similarly to what was mentioned with respect to other maternal factors, in order to decrease intrauterine infections it is important to address this issue in a comprehensive way, examining women’s societal role. In the case of maternal infections, potential interventions to decrease the risk to the offspring need to consider early screening and treatment.

**Other Environmental Influences on Fetal Growth**

Altitude is associated with diminished fetal growth due to lower ambient oxygen tension. However, in human populations there are multiple confounders that may obscure the relationship; for example, general populations living at higher altitude have been displaced from the more fertile lower valleys by the colonization process, so they have less access to quality foods, or are food insecure; they usually have more children, are of lower income and are less likely to have adequate sanitation. Exposure to ionizing radiation (X-rays) has been associated with microcephaly and abnormal fetal growth. Organic solvents and heavy metals, especially mercury and cadmium, have been associated with malformation and compromised fetal growth. Smoking, especially in the last trimester of pregnancy, reduces birthweight and length; the effect is proportional to the number of cigarettes smoked. Pre- and postnatal growth failure and microcephaly characterize the fetal alcohol syndrome. Growth restriction occurs in infants born to mothers addicted to heroin, cocaine or methadone. Other drugs with adverse effects include anticonvulsants (dilantin, phenobarbital and tegretol), antifolates (methotrexate), coumadin and prednisone. Some of these exposures may be not modifiable or at least not in an easy way (i.e. altitude); however, other factors such as exposure to pollutants or the consumption of toxic deleterious substances during pregnancy may be targeted through campaigns and directed follow-up of the pregnant women.
Interaction of Nutrients and Hormones during Perinatal Growth

Fetal growth also is affected by overall nutrition. Glucose supply, a key energy substrate, is also a mediator of insulin secretion; in turn, the action of insulin and insulin-like growth factors (IGF-1 and -2) affects fetal growth. Insulin regulates fetal lipogenic activity and has a permissive role in protein synthesis and hepatic glycogen deposition. Fetal hyperinsulinism results in increased adiposity in human infants of diabetic mothers. Conversely, fetuses with insulin deficiency secondary to pancreatic agenesis or with a defective insulin receptor have marked IUGR with decreased adipose tissue and little weight gain during the last trimester of pregnancy (Leprechaun syndrome).

Protein feeding as well administration of several essential and non-essential amino acids stimulates insulin secretion in the fetus and neonate. Increasing arginine levels during parenteral infusion has also been shown to increase serum insulin levels, lowering glucose and promoting growth hormone release by the anterior pituitary gland. The correlation of urinary excretion of the insulin precursor C-peptide with weight gain suggests that insulin behaves like a growth-promoting factor for infants on high-protein diets. Preliminary evidence from controlled clinical studies in extremely small preterm infants has shown increased tolerance to glucose and higher weight gain in infants infused with insulin during their initial postnatal days.

Other peptides such as insulin-like growth factors (IGF-1 and -2) act as growth factors influencing fetal growth and maturation. In the fetus, these act independently of growth hormone. IGF-1 influences terminal differentiation of a number of tissues, including brain astrocytes, neural outgrowth and myogenesis, and even though the influences of IGF-1 appears to be local; serum concentrations of IGF-1 correlate with birthweight. Both IGF-1 and -2 are complexed to binding proteins that modulate their biological activity. After birth, higher levels of IGF-1 are observed in IUGR infants during catch-up growth, especially in association with length gain. Epidermal growth factor and TGF-α also influence growth and differentiation of epithelial cells in lung and gut. Receptors for EGF are present throughout development and are increased in a number in placenta and lung in fetuses with growth restriction induced by uterine artery ligation, suggesting a role for EGF in fetal growth retardation. Maternal leptin, a circulating polypeptide hormone expressed by adipocytes and placenta, is positively related to fetal leptin concentrations affecting fetal weight. Additionally, thyroxin and glucocorticosteroids have important influences on specific organ development and functional and metabolic adaptation, but relatively little influence on fetal somatic growth. However, excess glucocorticoids as well as other hormones have been shown
to promote cell differentiation and maturation but arresting cell division, thus potentially compromising organ growth and development.

**Placental Nutrient Metabolism and Transport**

The placenta transfers metabolic substrates, oxygen and other nutrients from the mother to the rapidly growing fetus. In addition, the placenta allows for the excretion of fetal waste products and performs important metabolic and hormonal functions. The human fetal villi are directly bathed by maternal blood; therefore, the fetal capillary circulation is separated from maternal blood by placental vascular endothelium and connective tissue and the placental epithelium composed of the cytotrophoblast and the syncytiotrophoblast [37]. A clear understanding of placental ultrastructure is necessary in order to discuss the functional correlates.

The placenta grows at a very rapid rate during the initial stages of pregnancy. Placental growth is characterized by both increased numbers and branching of villi and microvilli and proliferation of the fetal capillary vessels in these villi. In this way, the surface area available for maternal-fetal exchange is greatly enhanced [38, 39]. Nutrients in maternal blood must cross the trophoblast cell layer and the basal membrane to reach the loose connective tissue surrounding the fetal capillaries. The uppermost layer of fetal tissues, the syncytiotrophoblast, is in direct contact with maternal blood. Microvilli increase the surface area necessary for nutrient transport [40]. Syncytial vacuoles are responsible for the transport of macromolecules and may be specifically targeted by cell surface receptors. The extensive endoplasmic reticulum and the high density of mitochondria provide the anatomical basis for both synthetic activities and transport through the cytoplasm of the syncytiotrophoblast. The multi-nucleated syncytiotrophoblast is the most important placental cell type in the second half of pregnancy and derives from the actively replicating cytotrophoblast. The syncytiotrophoblast represents the only uninterrupted cell layer interposed between the fetal capillary and maternal circulation.

**Placental Transfer**

Nutrient transfer occurs by simple diffusion, facilitated diffusion, active transport and receptor-mediated endocytosis, and is dependent on the surface area for exchange. Diffusion is determined by the concentration gradient of nutrients between fetal and maternal blood [41]. Most small molecules appear to be transferred by simple diffusion; these include water, sodium, urea, oxygen and carbon dioxide. A special case is the transport of glucose, the major energy substrate of
the fetus [42]. Glucose diffusion is selective and facilitated. Glucose transporter proteins have been described in the microvilli of the trophoblast facing the maternal decidua and the fetal capillary [43]. The transporters are not responsive to insulin [44]; they bind specifically to hexoses, have the highest affinity for glucose and are responsible for its active transport (requires energy and occurs against a concentration gradient). Similarly calcium [45], magnesium [46] and L-amino acids [47] have specific transport proteins. The transfer of intact proteins or other hydrophobic macromolecules is mostly mediated by pinocytosis or, more specifically, receptor-mediated endocytosis. The latter process requires a specific cell surface receptor and was initially described for the low-density lipoproteins. It has now been characterized for iron, folate, vitamin B₁₂, insulin and other macromolecules. This mechanism probably accounts for the transfer of IgG during the latter half of pregnancy. Transplacental transfer of IgG is highly specific and occurs at a faster rate than the transport of smaller proteins [48].

The fetus is totally dependent on placental circulation for the provision of substrates and other specific nutrients [49]. Later in gestation, fetal swallowing of amniotic fluid represents a non-significant additional transfer mechanism. As mentioned, glucose is transferred by selective facilitated diffusion. Of interest, the placenta metabolizes large amounts of glucose to lactate, and lactate, rather than glucose is likely the major precursor for fetal hepatic glycogen and fatty acid synthesis. Thus, the major sources of energy for the fetus, glucose and lactate, are transferred by diffusion. Gas exchange and fetal urea excretion occur by the same mechanism. In contrast, transfer of amino acids occurs against a concentration gradient and is energy dependent; circulating fetal amino acid levels are 30% higher than in the mother. In addition, L-amino acids are transferred more rapidly than the D isomers; except for IgG, intact proteins are not transferred across the placenta. Placental transport of lipids occurs mainly in the form of free fatty acids. Intact very low-density lipoproteins or low-density lipoproteins do not cross. During the last trimester of pregnancy, some of the increase in the fetal requirement for fatty acids is met by increased transport across the placenta. However, most fatty acid accretion is a product of fetal lipogenesis from non-lipid precursors. Essential fatty acid needs of the fetus are met solely by transplacental transport and reflect maternal dietary supply.

Considering the key role played by the placenta in fetal growth, careful examination of the placenta after birth may give us insights into the potential causes of IUGR as well as contribute in defining future risks of the baby. In some settings, the placenta may not be available for examination since it is used in rituals after the birth of the child; however, it should still be relatively easy to examine it immediately after the placenta is expelled. If we are to make use of the placenta as an indicator of normal fetal growth and future health of the baby,
there is a need to systematize its observations and define what measurements will be obtained beyond weight. It would be of potential benefit to this field to establish a common protocol to assess shape, key diameters, thickness, cord insertion and characteristics at the time of birth, including vessels, chorion and amnion on the fetal side, as well as structure and vascular indemnity of the cotyledons on the maternal side. This might prove of critical importance in defining the predictive value of the different findings in different categories of IUGR.

Since we have limited information on the mechanisms involved in fetal programming, the possibilities for treatment or intervention opportunities are for now limited. This is the case of interventions that could eventually lead to changes in placental structure, area or function. The association of IUGR and limited placental transport has been extensively described, and therefore enhancing placental transport in IUGR potentially could improve fetal growth and development. Several groups have shown benefits of maternal IGF-1 infusion on placental and fetal growth; the mechanisms shown in vitro suggest an important role for this key growth factor in trophoblast glucose and amino acid uptake. On the other hand, maternal IGF-2 infusion in guinea pig stimulates fetal growth by affecting the placental structure, rather than its transport capacity [50]. A limitation of these studies is that they were conducted in normal pregnant mammals, and not on animals affected by placental insufficiency or IUGR. Other possible but more speculative interventions focus on stimulating the placental L-amino acid transporter system responsible for transferring multiple essential amino acids through mTOR; administering low doses of atrial natriuretic peptide has been shown to selectively dilate placental circulation. Finally, the option of altering the methylation status of important placental genes such as 11-β-HSD-2 involved in oxidative/nitrative stress through maternal folate supplementation has been postulated.

Glucose is the major energy substrate for the fetus and the newborn, although the fetus is capable of utilizing lactate, free fatty acids or ketone bodies under special conditions. Glucose is able to induce its own non-energy-dependent transporters, appropriately named the GLUT1–7 family [42, 43]. The variation in GLUT isoform expression during development is time and tissue specific. GLUT1 is expressed in virtually every fetal cell except neurons; it accounts for most basal glucose uptake. GLUT3 is a high-affinity transporter found in the placenta. In situations of maternal glucose scarcity, this transporter may be capable of scavenging maternal glucose for use by the placenta and the fetus. The expression of insulin-sensitive GLUT4 appears late in gestation in cardiac and skeletal muscles, and in adipocytes. Glut 1 is expressed to a greater extent in fetal than adult lung. Normal insulin/cortisol ratios stimulate glucose transport while high insulin/cortisol ratios inhibit glucose uptake. This hormone balance delays lung maturation in infants of diabetic mothers that have a high circulat-
ing insulin and promotes lung maturation in IUGR infants that have lower insulin and higher cortisol levels.

The high glucose demand of the brain is successfully met by a combination of GLUT3 and GLUT1 and a hexokinase with a higher affinity for glucose than its counterpart in liver, muscle or kidney, thus favoring glucose uptake by the brain. During fetal life, GLUT1 constitutes the main brain glucose transporter, while GLUT3 appears after birth. Glucose transport may also be mediated by the Na-glucose-linked transporter family that actively transports glucose in polarized intestinal and renal epithelial cells. Glucose/Na cotransporters appear to be active prenatally; thus, the intestine is ready to absorb glucose with the first feed.

**Energy Stores**

Fetal liver progressively increases its glycogen concentration throughout gestation reaching a maximum of 10% of organ weight at the time of birth. However, in the full-term newborn, glycogen stores provide a reserve of ~100 kcal, barely sufficient to provide the basal energy needs of a full-term infant for 8–10 h. In extremely low-birthweight infants, glucose supply runs out in minutes. Preterm babies are therefore susceptible to hypoglycemia. Since liver, skeletal muscle and heart are able to oxidize free fatty acids derived from adipose tissue, adipose tissue represents the main energy reserve for the normal newborn. This is explained in part by the greater energy released by fat oxidation (1 g of fat yields 8–9 kcal) and also by the fact that triglycerides are stored in a water-free environment giving adipose tissue an energy density of around 8 kcal per gram, as opposed to 1 kcal per gram of liver. Only a third of the energy reserve from protein is available as an energy source; lean body mass losses in excess of 1/3 are associated with adverse functional consequences. This information allows for a quantitative assessment of energy reserves for the fetus and has been linked to the survival potential under conditions of semi-starvation such as the IUGR fetus. A full-term infant has enough energy reserve to support its needs for several weeks. An infant with a birthweight under 1,000 g has reserves for only a few days [49].

**Lipid Metabolism**

Most fetal triglycerides are derived from fatty acids produced in the fetal liver and placenta since fatty acid transport is meager and lipoprotein transfer from the mother is insignificant or nonexistent [51]. Of interest, the fetal brain and lung are also capable of lipogenesis to produce the unique lipids important for
As fetal plasma fatty acids enter adipocytes and are re-esterified to triglycerides, adipose tissue exhibits dramatic growth during the last trimester of pregnancy. A 27-week fetus has only 1% of its bodyweight as fat, whereas the figure is 16% in the normal full-term infant. Substantial quantities of fetal body fat, especially that located in the vicinity of the major large vessels, are metabolically active. This fat is rich in heme-containing cytochromes and mitochondria and hence is brown in color. Its function is to produce heat. Lipid vesicles provide the fatty acids for oxidation, and the mitochondria possess a specific protein that uncouples aerobic fuel oxidation from ATP formation, producing heat. Activation of this non-shivering thermogenesis is triggered by sympathetic stimulation of lipolysis. With advancing postnatal age, shivering thermogenesis is established. Most brown fat involutes or becomes white fat.

The brain is unable to oxidize free fatty acids directly, and therefore relies mainly on glucose as a substrate. Fat can be oxidized indirectly, after conversion to ketone bodies if the concentration is high enough. The ability of the newborn liver to generate large amounts of ketone bodies is not present at birth and takes several days to develop. The maintenance of cerebral metabolism on an acute basis is therefore dependent on liver glycogen stores and gluconeogenesis in the liver and the kidney. Alanine and glutamine, generated from protein breakdown, and lactate and glycerol are the predominant gluconeogenic substrates. Ketone body oxidation and gluconeogenesis enable the newborn to maintain glucose homeostasis under the conditions of fasting or semi-starvation typical of early postnatal life. Early postnatal diets supplement and complement these responses. Human milk is uniquely suited for this purpose. It contains lactose and substantial amounts of easily absorbable medium-chain triglycerides. Even long-chain triglycerides in human milk have a special molecular configuration which makes them easier to digest. In addition, human milk provides the carnitine necessary for mitochondrial fatty acid transport and ketone body production, as evidenced by higher levels of plasma ketone bodies in babies fed human milk.

Metabolic regulation in the newborn period is based on substrate availability and the endocrine response induced by these substrates. During fetal life, after the 20th week of gestation, the fetal pancreas produces insulin. This hormone regulates the accumulation of glycogen in liver, muscle and lung. At the same time, it promotes lipogenesis and triglyceride storage within adipose tissue. Insulin also enhances protein synthesis in muscle. The action of insulin is modulated by glucocorticoids, which regulate gene expression and induce various enzymes related to glycogen and lipid synthesis. Steroid hormones are responsible for the induction of glycogen synthetase type I which is activated by insulin and responsible for glycogen synthesis. Fetal steroid hormone concentrations are
low throughout much of gestation. This explains why, despite detectable circulating insulin after 13 weeks of gestation, glycogen accumulation does not occur until the 27th week.

At the time of birth, the constant supply of maternal glucose is interrupted, and the infant’s blood glucose concentrations decrease. As a result, insulin levels fall and glucagon increases. The ratio between insulin and glucagon is essential in the regulation of gluconeogenesis and glycogenolysis. The hepatic intracellular signaling cascade induced by glucagon responds exponentially such that small changes in glucagon induce large changes in glycogenolysis and glucose availability. Glucagon and cortisol promote gluconeogenesis. Glucagon and catecholamines, in addition to activating glycogen breakdown pathways, promote lipolysis, generating glycerol, a gluconeogenic precursor, and free fatty acids. Free fatty acids directly and indirectly provide an alternative to glucose as oxidative fuel (see above). High glucagon and cortisol and low insulin favor protein catabolism, especially skeletal muscle protein breakdown, yielding amino acids for gluconeogenesis [52].

The postnatal changes in respiratory quotient, defined as the ratio between carbon dioxide production and oxygen consumption, reflect the postnatal fuel transition from glucose to a mixture of glucose and fat. A respiratory quotient of 1.0 corresponds to predominant use of glucose as a fuel for oxidation. A value of 0.7 corresponds to exclusive fatty acid oxidation.

Thyroxine and growth hormone promote lipolysis and further potentiate gluconeogenesis. Arginine vasopressin (AVP) has also been shown to induce a hyperglycemic response in the fetus. AVP is released during fetal stress and may represent a major modulator of fetal metabolism in addition to regulating cardiovascular responses.

In summary, the goal of neonatal glucose homeostasis is to provide the brain and other vital organs with sufficient glucose as a key energy source. Virtually all hormones except insulin will increase glucose, which is then taken up preferentially by the brain. The sequence described in this section constitutes the basis for perinatal glucose adaptation and can be verified in virtually all mammalian species.

**How to Achieve Optimal Fetal Growth**

The development of growth parameters to be used as a ‘gold standard’ is important not only for medical use in individual clinical monitoring; it is also critical because inadequate standards will have major unintended and possibly detrimental consequences on the health of future generations. Using the wrong growth charts to monitor fetal growth and size can, for example, result in an in-
crease in maternal antenatal hospitalization, unjustified intensive neonatal care, increase in induction of labor and cesarean sections which will impose risks on mothers and children, or at the very least on mothers, without benefiting either.

Recently, the International Fetal and Newborn Growth Consortium (INTERGROWTH 21st) have taken the responsibility of developing growth charts with a prescriptive approach [53, 54]. The study succeeded in its ambitious agenda and will provide us not only with well-timed fetal measures of gestational age confirmed by early US taken at 9–13 weeks, but will also provide us with 6 serial US assessments. The selected sites of US measurements were: (a) placental localization and fetal presentation, amniotic fluid volume index, (b) two head diameters (BPD and OFD) and head circumference, (c) transverse and anteroposterior abdominal diameters and circumference, (d) femur length obtained under strict quality controls to ensure the validity and precision of the data collected.

INTERGROWTH will provide clinicians and researchers with sequential longitudinal data that will serve to characterize whole body as well as brain, liver, and long bone growth, giving us the possibility to relate this to placental blood flow and transfer function, neonatal health, morbidity and mortality. The proposed normative fetal growth standards will represent a quantum leap in terms of evaluating the effect of early-life events on later growth, health and well-being. The INTERGROWTH study used a large, contemporary, representative, and multi-ethnic sample; a critical issue is to define ‘optimal’ environmental conditions. This is particularly difficult in the case of intrauterine growth standards since fetal nutrition depends not only on maternal conditions but also on the indemnity and functional state of the fetoplacental unit as we have already discussed. It is likely that in the future we will learn more about the true determinants of fetal growth and how these may condition long-term health and disease. In order to address this issue, the INTERGROWTH group defined a minimum set of sociodemographic (i.e. maternal education, assets, age, etc.), health (i.e. presence of gestational diabetes, history of stillbirths, etc.), nutritional (i.e. adequate weight status and diet), and environmental exposures (i.e. smoke, pollutants, etc.) as a prerequisite for all subjects entering the study. The adequacy of the prescriptive approach in developing the standard will be finally evaluated by linking the impact of the ‘new standard’ on short (i.e. neonatal morbidity and mortality, cognitive development) as well as long-term outcomes (i.e. disability, obesity, cardiovascular diseases).

The results of the INTERGROWTH prescriptive standards, soon to be reported, will serve to objectively define normal fetal growth; it represents great progress. It will not only give us well-timed fetal measures since gestational age was confirmed by an early US taken at 9–13 weeks, but will also provide serial US assessments of (a) placental localization and fetal presentation, amniotic fluid volume index, (b) two head diameters (BPD and OFD) and head circumference, (c) trans-
verse and anteroposterior abdominal diameters and circumference, (d) femur length that will be obtained under strict quality controls to ensure the validity and precision of the data collected. Thus, for the first time clinicians and researchers will have sequential longitudinal data that will serve to characterize whole body as well as brain, liver, and long bone growth relating this indirectly to placental blood flow and transfer function, neonatal health, morbidity and mortality. The proposed fetal growth standards will represent a quantum leap in terms of evaluating the effect of early life events on later growth, health and well-being.

The study used a large, contemporary, representative, and multi-ethnic sample. However, a critical issue in the generation of the INTERGROWTH standard is how to define ‘optimal’ environmental conditions. In the case of intrauterine growth, this is further complicated by the fact that fetal nutrition depends not only on maternal conditions but also on the indemnity and functional state of the fetoplacental unit. It is likely that in the future we will learn more on the determinants of fetal growth and how these may condition long-term health and disease. However, in the meantime it seems reasonable to consider a minimum set of sociodemographic (i.e. maternal education, assets, age, etc.), health (i.e. presence of gestational diabetes, history of stillbirths, etc.), nutritional (i.e. adequate weight status and diet), and environmental exposures (i.e. smoke, pollutants, etc.) in defining what it is ‘optimal’.

Disclosure Statement

All authors declare that no financial or other conflict of interest exists in relation to the content of this chapter.

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