Human fetal growth and organ development: 50 years of discoveries

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Knowledge about human fetal growth and organ development has greatly developed in the last 50 years. Anatomists and physiologists had already described some crucial aspects, for example, the circulation of blood during intrauterine life through the fetal heart, the liver as well as the placenta. However, only in the last century physiologic studies were performed in animal models. In the human fetus, the introduction of ultrasound and Doppler velocimetry has provided data about the growth and development of the fetus and of the circulation through the different fetal districts. Moreover, in the last 2 decades we have learned about fetal oxygenation and fetal nutrient supply caused by the availability of fetal blood samples obtained under relatively steady state conditions. These studies, together with studies using stable isotope methodologies, have clarified some aspects of the supply of the major nutrients for the fetus such as glucose, amino acids, and fatty acids. At the same time, the relevance of placental function has been recognized as a major determinant of fetal diseases leading to intrauterine growth restriction. More recently, the availability of new tools such as 3-dimensional ultrasound and magnetic resonance imaging, have made possible the evaluation of the growth and development of fetal organs. This knowledge in the healthy fetus will improve the ability of clinicians to recognize abnormal phenotypes of the different fetal organs, thus allowing to stage fetal diseases.

In the 1950s obstetricians knew very little about intrauterine life, and delivery often represented a surprise, for example, with the birth of twins or malformed fetuses.

A progressive walk backwards, from delivery to conception, started at that time, leading today to a much deeper knowledge of intrauterine growth and development, of fetal organs (both in terms of anatomy and function) and of fetal diseases (considering causes and natural history).

But the “long obstetric walk” could have been easier and faster by: (1) taking into account previous lessons of anatomists and physiologists into a form of comparative obstetrics and by (2) starting from considering the fetus as a healthy person rather than focusing from the beginning on fetal abnormalities (generalized as fetal distress). Obstetricians have instead learned at first by studying fetal diseases and this wrong attitude has led to hurried statements, such as “the fetus as a patient.”
must, on the contrary, start by the understanding of what is the healthy condition, and this has to be the goal of obstetrics today.

The lesson from anatomy

Much of the knowledge that we have today on anatomy of different fetal organs has been known and described by anatomists for many years. In the 16th and 17th century, both Aranzio and Harvey were aware that the uterine (maternal) and umbilical (fetal) blood vessels were not directly connected with one another within the placenta. Moreover, once Harvey established the fact that the blood circulated, it was clear that the 2 great fetal channels, the foramen ovale and the ductus arteriosus, enabled the 2 ventricles of the heart to work in parallel, pumping the blood from the great veins to the arteries. At the same time, it became evident that some of the arterial blood circulated to the fetal tissues and the remainder to the placenta.

In the 18th century, Wolff supposed that about two thirds of inferior vena caval blood flow might enter the left atrium through the foramen ovale, the remainder entering the right atrium. He did not believe that the Eustachian valve was an essential feature of the fetal circulation, and he clearly visualized mixing of 2 caval blood streams within the right atrium, although only inferior vena caval blood entered the left atrium.

In 1564, before the fetal circulation hypothesis by Wolff, Vesalius published the first account of the ductus venosus, incorrectly attributed to Aranzio. The ductus venosus originates from the trunk created by the umbilical vein and the portal vein and runs almost surrounded by the substance of the liver to the junction of the main hepatic veins with the inferior vena cava. Vesalius recognized that it was less than half as wide as the umbilical vein and demonstrated the outflow of the ductus venosus directly in the right atrium. In 1753, Bertin used wax injections to study the relation of the ductus venosus to the hepatic vessels. However, until 50 years ago few direct observations have been made on the living mammalian fetus, either in utero or after delivery. Rudolph et al have elegantly described the fetal hepatic vasculature and blood flow in fetal lambs by silicone rubber injection. In the fetus, the liver blood flow is derived from the umbilical vein, as well as from the portal vein and hepatic artery. The umbilical vein enters the hepatic hilum and gives portal branches to the left lobe of the liver. The ductus venosus then arises, while the umbilical vein arches to the right, where it is joined by the portal vein then giving rise to portal branches to the right liver lobe. The left hepatic vein joins the ductus venosus immediately before the connection with the inferior vena cava, while the right hepatic vein connects separately to the inferior vena cava. Studies in animal models performed by Rudolph et al have led the way to more recent studies using Doppler methodologies that have evaluated and described the circulation and distribution of blood flows in the various organs of the human fetus. These studies very clearly illustrated the main patterns of the fetal circulation.

The lesson from physiology

To consider the fetus as a healthy individual, we have to start by looking at specific organs physiology. In the 1940s, Barcroft calculated basal oxygen consumption of a number of tissues of the sheep fetus at different gestational ages, showing that this value increased in the fetal brain from 3.4 (at 99 days) to 8.3 (at 144 days) mL/mg dry weight per hour, while it decreased in tissues such as the muscle (from 3.1-0.7 mL/mg dry weight per hour) and it stayed quite stable in the liver (around 7.3 mL/mg dry weight per hour). Later on, Battaglia and Meschia calculated uterine and umbilical oxygen uptakes in the chronically catheterized pregnant sheep, reporting values of 2.16 mmol/min as uterine oxygen uptake, 1.18 mmol/min as umbilical oxygen uptake, and thus obtaining a value of 0.98 mmol/min as utero-placental O2 use. These observations obtained in vivo underline the very high metabolism of the placenta, consuming almost as much oxygen as the fetus.

Recently, improvements of ultrasound technologies have made possible the measurement of umbilical blood flow in human pregnancies in utero. The umbilical vein volume flow is calculated from the umbilical vein area and the umbilical flow velocity (Figure 1). By these means, umbilical blood flow has been measured in the second half of normal pregnancies, yielding values ranging between 70 and 100 mL/kg/min at term. We then estimated umbilical oxygen uptake as the product of umbilical blood flow and umbilical O2 venoarterial difference. In normal term human pregnancies, fetal oxygen consumption can then be estimated with values ranging between 0.25 and 0.35 mmol/min/kg or 0.9 and 1.2 mmol/min, similar to the values obtained in the sheep.

Considered from the standpoint of the placenta, an important measurement is the difference in pressure between umbilical artery and vein, representing the driving force for blood into the placental vessels. Measurements of arterial pressure have up to now only been possible in animal fetuses and we have no direct measurement of blood pressure in the umbilical circulation or in the fetal districts. However, even in animal models, some discrepancies have been observed in relation to the technique used for the measurement. With all due corrections, however, Barcroft was able to demonstrate that throughout gestation arterial pressure increases while venous pressure stays pretty constant, thus granting a gradient that rises from an average of...
15 mm Hg at 60 days to an average at birth around 40 mm Hg.

In human pregnancies, changes in uteroplacental perfusion have been indirectly measured in the last 2 decades by investigation of blood flow profiles through Doppler velocimetry. By these means, reduced blood flows have been demonstrated in both the uterine and umbilical arteries in intrauterine growth restriction (IUGR). Such measurements, particularly in regard to the umbilical circulation, have made a significant contribution to recent advances in the management of high-risk pregnancies. In normal pregnancies, branches of the uterine arteries are converted into low-resistance uteroplacental vessels. Alterations in this process have been observed on placental bed biopsy specimens from IUGR pregnancies and are associated with evidence of bilateral high-resistance flow velocity waveforms with early diastolic notches at 24 weeks of gestation. Abnormal umbilical artery Doppler waveforms are thought to reflect deranged placental impedance secondary to altered vessel morphology in the villi and show a strong association with increased perinatal mortality.

Measurements of arterial blood pressure coupled with umbilical arterial Doppler velocimetry profiles have been recently performed in chronically catheterized pregnant sheep with induced IUGR by the heat chamber model developed in Denver. Compared with control pregnancies, IUGR pregnancies showed elevated systemic blood pressure, reduced umbilical blood flow, elevated umbilical arterial and aortic Doppler velocimetry indices, and increased placental vascular resistances. Very interestingly, the umbilical arterial Doppler index of resistance (systolic/diastolic ratio) correlated strongly with systemic blood pressure (Figure 2). This whole animal study shows that IUGR fetuses are hypertensive and that increased umbilical arterial Doppler resistance indices are consistent with a fetal-placental hypertensive state. Very likely, the later stages of the disease, when the heart flows are affected, are associated with decreases in blood pressure. Changes in fetal blood pressure could lead to permanent changes in the cells lining the umbilical cord and the fetal vessels and be related to the increased risks for cardiovascular pathologies in adult life, strongly related to growth before birth. Recently, changes in genes involved with regulation of blood flow have been observed in endothelial cells of the umbilical vein in conditions of hypoxia and in diabetes.

The development of vascular reflexes has also been a subject of investigations by fetal physiologists. Studies in goat fetuses on changes in arterial blood pressure showed that shortly after the ligature of the umbilical cord, at or near term, the fetal heart slows. This is of course common practice in clinical obstetrics. However,
it is common thought that this is due to asphyxia leading to heart block. Barcroft has elegantly demonstrated, by vagi cut, how at least the first part of the decrease in heart rate, during variable decelerations after cord compression, is related to vagal activation.

Further knowledge about fetal responses to changes occurring during fetal decelerations came also from studies on fetal heart conduction times. Modifications of the P wave and of the PQ interval have been reported during variable decelerations, when the fetal heart rate falls to levels between 80 and 60 beats/min for more than 10 to 20 seconds. At the beginning of the deceleration the PQ interval becomes progressively shorter and then the P wave becomes biphasic or completely disappears. These changes suggest that vagal mechanism is involved, leading to a depression of the sinoatrial node with wandering pacemaker, and the control of the rhythm is assumed by the atrioventricular node.

Placenta (volume, circulation, fetoplacental metabolism)

If we now consider the fetal organs, we must start from the placenta, which can be studied as far as volume, circulation, and fetoplacental metabolism are concerned.

Volume

The growth of the placenta is quite different from that of the whole fetus. In sheep, Barcroft described more than 50 years ago that, considered in respect to gestational age, fetal weight increases substantially in the second half of pregnancy, whereas cotyledons grow rapidly in the first half and then stay pretty stable until the end of pregnancy. Evidence that the placenta reaches its maximum size mostly well before term has been provided also for other species, such as the goat and the rabbit. In human pregnancies, the different growth patterns of fetus and placenta are accompanied by a large increase in the fetal/placental weight ratio during gestation. However, in contrast to sheep in which placental weight peaks at mid gestation, in the human placental growth follows an S-curve regression, whereas fetal growth follows an exponential pattern with maximum growth in the third trimester. The growth of the placenta is accompanied by a number of maturational changes including significant increases in total placental surface area and decreased thickness that together lead to increased placental permeability to nutrient substrates. In addition, significant changes have been observed in the activity of a number of placental transport systems in relation to gestation, with most changes occurring in the microvillous membrane after the first trimester.

Recently, the evaluation of placental volume and growth has become possible during pregnancy by means of 3-dimensional (3D) ultrasound, as shown in Figure 3. Placental volume increases from average values of around 16 mL at 10 weeks to 200 mL at 23 weeks. Therefore, the ratio between fetal and placental weight is approximately 2 at 23 weeks compared with values around 6 at term in normal pregnancies. Interestingly, 17 chromosomally abnormal fetuses (carriers of trisomy 21) showed decreased placental volumes compared with normal fetuses of similar gestational age (Figure 4). Studies at term, have shown that small-for-gestational-age infants have smaller placentae and a reduced placental to fetal weight ratio than normal fetuses of the same birthweight. Preliminary data from our group show that although in normal pregnancies, lower placental weights are not associated with significant decreases in fetal weights, in IUGR pregnancies there is a steeper relationship between lower placental weights and decreases in fetal weights, particularly in the most severe IUGR. At the opposite end, increased placental weights and placental to fetal weight ratios have been reported in pregnancies complicated by gestational diabetes, even in the presence of optimal maternal glycemic control throughout the third trimester. It is therefore promising that measurement of placental volume in the second trimester of pregnancy has been shown to correlate significantly with birthweight.

Circulation

The degree of correspondence between the uterine and the umbilical placental perfusion is crucial for efficient exchanges and defines the so-called even or uneven placental perfusion. In the ideal situation, an even perfusion system is represented by proportional flows of the uterine and umbilical circulations. The uneven circulation is represented by a mismatch so that a placental cotyledon is
perfused in different proportions on the uterine and umbilical side thus determining inefficient exchanges. We still do not have tools to evaluate this functional condition in human pregnancies, and we do not know what happens in vivo in pathologic situations like placental infarction.

Another interesting aspect of uterine and umbilical perfusion is whether the 2 circulations represent a countercurrent or a concurrent system. The arrangement between uterine and umbilical vessels has been described in cotyledons of sheep’s placenta. The maximum efficiency would be obtained with 2 capillary streams running in opposite directions, with umbilical arterial values equilibrating with uterine arterial ones. However, this does not seem the case in human pregnancies. We have simultaneously measured blood gases in the arterial and venous vessels of the uterine and umbilical circulation at the time of elective caesarean section in term human pregnancies. As shown in Figure 5, umbilical venous pO2 was positively correlated to and always lower than uterine venous pO2, thus suggesting that the human placenta is a prevailing concurrent system, with equilibration between the 2 venous placental outflows. Moreover, IUGR pregnancies were characterized by a significantly increased gradient between the uterine and the umbilical vein compared with normal pregnancies. Because the uterine coefficient of extraction of oxygen was significantly decreased, leaving high levels of oxygen in the uterine vein leaving the pregnant uterus, taken together these data suggested that the decreased oxygen levels observed in IUGR fetuses were apparently reflecting a problem of placental permeability, rather than of placental perfusion.

However, in our experience hypoxia is not a constant feature of IUGR. Rather, according to a classification of IUGR based on Doppler velocimetry of the umbilical artery and fetal heart rate, we have shown that hypoxia and hyperlactacidaemia are present in one third of fetuses with increased pulsatility index of the umbilical artery and in two thirds of those with abnormalities of both umbilical blood flow and fetal heart rate.

**Fetoplacental metabolism**

During intrauterine life, the placenta represents an organ interfacing the fetus with the mother, thus being essential to nutrition before birth. The placenta is therefore a fetal organ, although when considering fetal nutrition, pregnancy can be viewed as a 3-compartment
model, with the mother, placenta, and fetus each presenting their own metabolism while interacting with each other. From a nutritional point of view, the fetus depends from the maternal supply of nutrients through the placenta into the umbilical circulation. Fetal growth is regulated by the balance between the fetal nutrient demand, determined by its genetic growth potential, and the maternal-placental supply. Factors that determine the maternal-placental supply of nutrients include maternal nutrition and metabolism, maternofetal concentration gradient, uteroplacental blood flow, placental size, and its transfer capabilities.

Glucose, amino acids, and fatty acids represent the most important nutrients in fetal life, both for tissue deposition and as fuels for oxidative purposes. It is impossible to separate placental metabolism from maternal and fetal metabolism, as the placenta is located in the middle of a number of metabolic processes. However, we must keep in mind that the placental cell, ie, the trophoblast cell, is a fetal cell. This reflects the fact that the placenta is part of the fetal system, thus receiving and providing feedbacks to the fetus.

Much of what we know concerning nutrient supply in human fetuses has been described in the last 20 years from data obtained at the time of fetal blood sampling. We have described that umbilical venous oxygen content is quite stable in the second half of gestation. This is the result of a concomitant significant increase in hemoglobin concentration and a decrease in pO2 in umbilical venous blood.

A facilitated diffusion system is responsible for maternal to fetal transfer of glucose, mediated by members of the glucose transporter (GLUT) family, which are localized on both maternal and fetal facing membranes. In normal pregnancies, fetal glucose concentrations are strictly dependent on both maternal concentrations and gestational age, with the placenta itself consuming a considerable amount of glucose. IUGR fetuses do not present on average decreased glucose concentrations compared with normal fetuses. Moreover, we were not able to observe any significant glucogenesis in the fetal compartment during maternal continuous infusion of UL-13C-glucose in IUGR pregnancies undergoing fetal blood sampling. However, fetal-maternal gradients for glucose are significantly increased in those fetuses that show an impairment of umbilical arterial blood flows and fetal heart rate. On the other hand, preliminary observations in vivo report that umbilical venous glucose concentrations are significantly increased even in well-controlled gestational diabetes mellitus (GDM) pregnancies, with maternal substrate levels comparable to those observed in normal pregnancies. This could either indicate a contribution of increased placental transport or an alteration of fetoplacental metabolism for glucose in pregnancies with GDM.

The transfer of fatty acids from the mother to the fetus is much more complex. Although the fatty acid mix delivered to the fetus is largely determined by the

![Figure 4](image1.png) Placental volume measures in normal (●) and chromosomally abnormal (○) fetuses between 10 and 24 weeks of gestation.

The fatty acid composition of the maternal blood, the placenta is able to preferentially transfer arachidonic acid (AA) and docosahexaenoic acid (DHA) to the fetus, which is carried out by means of the combination of several mechanisms. Although all fatty acids can cross lipid bilayers by simple diffusion, a number of fatty acid binding proteins (FABPs) have been identified. Essential fatty acids are mainly provided to the placenta by not-esterified fatty acids carried by triglycerides from lipoproteins of maternal adipose tissue and liver. They are released by way of lipoprotein lipase (LPL), whose activity was demonstrated in human placenta.

We have recently shown that the levels of expression of LPL messenger RNA (mRNA) are significantly increased in IUGR, particularly in those IUGR that show impairment of umbilical arterial blood flows. Differently from our results, Magnusson et al previously reported reduced LPL activity in placental microvillous membranes (MVM) in IUGR cases. Therefore, it is possible to speculate that, also in presence of reduced LPL activity, LPL mRNA expression might be increased as a compensatory mechanism. Alterations of LPL expression could be associated with changes in fatty acids placental exchange and might contribute to the abnormal polyunsaturated fatty acids fetomaternal relationships reported in IUGR pregnancies undergoing fetal blood sampling.

Placenta also contains specific binding sites for lipoproteins (very low density lipoprotein [VLDL], LDL, high density lipoprotein [HDL]) that carry esterified lipids. Alterations in receptors involved in placental cholesterol uptake have been reported in severe forms of IUGR, associated with changes of LDL and cholesterol in the maternal circulation.

A great deal of studies have demonstrated a range of clearly defined placental alterations in pregnancies associated with IUGR, and this is becoming apparent also in the presence of excess of fetal growth. These changes have been quite well described for amino acids both in vivo and in vitro, with decreased amino acid concentrations and placental transporters activity in IUGR pregnancies and increased concentrations and transport in diabetes.

Amino acids cross the placenta with complex mechanisms that include the activity of transporters located on both the MVM and basal membranes, placental metabolism as well as neosynthesis within the placenta for nonessential amino acids. The result of these complex mechanisms is an active transport, so that amino acid concentrations are higher in the fetal than in the maternal circulation throughout the second half of pregnancy. In IUGR pregnancies, we reported significantly lower concentrations, particularly for the essential branched chain amino acids, independently from the degree of severity, with significantly reduced fetal-maternal ratios.

The kinetics of these mechanisms have been investigated in vivo under steady state conditions by giving a constant infusion of $^{13}$C-leucine to the mother before fetal blood sampling. Figure 6 presents these results in normal pregnancies and in IUGR divided according to severity. In normal pregnancies, because leucine is an essential amino acid, the dilution (by approximately 20%) of the tracer in the fetal circulation is accounted for by protein catabolism. This component, however, is significantly and progressively increased in IUGR pregnancies, indicating that, besides a reduction in placental transport, also protein catabolism is proportionally increased in IUGR; and maybe considered a sign of fetal decompensation.
These evidences have led to the concept that the alterations in the human placenta can be grouped into patterns, or phenotypes, associated with specific types of fetal growth. Identifying the placental phenotypes of different fetal growth patterns should improve the comprehension of fetal growth and also help clinicians to identify pregnancies at risk for fetal growth abnormalities.

**Heart and circulation**

Fifty years ago, Dawes calculated that cardiac output in the fetal lamb is 315 mL/kg/min. Of these, 142 mL/kg/min (45%) originate from the right ventricle and 174 mL/kg/min (55%) from the left ventricle. In the human fetus, by measuring peak velocities in the heart vessels, we have calculated a blood flow of 600 mL/min in the pulmonary artery and 450 mL/min in the aorta. The sum of these 2 measures yields an approximate value of 1050 mL/min, or approximately 300 mL/min/kg, remarkably similar to the values reported by Dawes in the fetal lamb.

Besides cardiac output, today we are able to evaluate the distribution of blood to the different organs in the human fetus, such as the umbilical, cerebral, hepatic, and cardiac districts. By these means, the temporal sequence of abnormal Doppler changes in the fetal circulation has been described in a subset of early and severely growth-restricted fetuses. In this study, severely growth-restricted fetuses followed a progressive sequence of acquiring Doppler abnormalities that were categorized into “early” and “late” Doppler changes. Early changes occurred in peripheral vessels (umbilical and middle cerebral arteries; 50% of patients affected 15-16 days before delivery). Late changes included umbilical artery reverse flow, and abnormal changes in the ductus venosus, aortic and pulmonary outflow tracts (50% of patients affected 4-5 days before delivery). These progressive alterations represent the natural history that in fetal diseases associated to growth restriction starts with fetal adaptation and then proceeds into failure. Late changes are indeed significantly associated with perinatal death and should prompt delivery.

**Fetal organs**

Most of the knowledge that we have today about intrauterine life has been built around the placenta and the fetal heart and circulation. This is principally the result of availability of tissues (for the placenta) and of techniques (evaluation of fetal heart rate and Doppler evaluation of blood flows).

Figure 8  Technique of liver volume determination by 3D ultrasound.
However, new technologic tools open new perspectives in the study of fetal organs development and function. We now focus and report available data about brain and liver, 2 of the most important fetal organs.

Brain

The relevance of fetal brain growth and development is evident from the simple observation that the ratio between brain and body weight is significantly higher in newborn infants than in adults in all species, but particularly in the human.\(^{56}\)

The growth of the brain has been evaluated by measuring its volume through 3D ultrasound, showing that median brain weight represents approximately 15% of total fetal weight. Sonographic measurement of fetal brain volume demonstrated a nearly 10-fold increase during the second half of gestation.\(^{57}\) In fetal diseases such as IUGR, brain growth is preserved even when there is a reduction in umbilical blood flow, with a reduction in brain volume growth proportionally much less of what occurs to other organs like the liver.\(^{8}\)

Magnetic resonance imaging (MRI) represents a powerful technique for evaluation of fetal brain development and function. In particular, the measurement of water apparent diffusion coefficient in the human brain by means of diffusion-weighted (DW) MRI has provided valuable information in normal cerebral development providing information about the size and course of unmyelinated as well as myelinated tracts in the fetal brain in the second half of pregnancy.\(^{58}\) Bands of migrating glia can be visualized and represent very important markers of normal brain development, in particular of the white matter.\(^{59}\) The uniform appearance of periventricular bands and their relationship to the infants’ maturity is consistent with the results of histologic studies (Figure 7).\(^{60}\) These MRI studies demonstrate the presence of migrating glial cells within the periventricular white matter of infants beyond 20 weeks’ gestation, when neuronal migration to the cortex is complete. Moreover, although prenatal ultrasound has a low sensitivity in the detection of hypoxic-ischemic damage, recently prenatal DW MRI has been shown to allow the diagnosis of acute fetal brain ischemic lesions in utero.\(^{61}\)

Today, however, the best available tool for the evaluation of neurologic integrity is still represented by fetal heart rate analysis. Fetal heart rate variability must indeed be considered as an indicator of neurologic rather than of cardiac function. A mean variability below 1 beat/min strongly suggests the disappearance of heart rate control by the autonomic nervous system and must be viewed as a sign of central nervous system lesion.\(^{62}\)

Fetal liver

As already discussed in the section on Heart and circulation, the fetal liver is located at a very special circulatory crossing. Moreover, the fetal liver is involved in numerous metabolic processes, as well in metabolic and endocrine cycles with the placenta. The evaluation of fetal liver growth and function is therefore of utmost importance in understanding fetal physiology and in the evaluation of fetal well being. Fetal liver volume has recently been evaluated in utero by 3D ultrasound, as shown in Figure 8. By these means, the growth of liver volume in normal fetuses from 18 weeks to term has been shown to follow an exponential curve.\(^{7}\) At the same time, evidence has been provided that fetal diseases that lead to alterations of fetal growth are associated with proportional changes of fetal liver volumes. Decreased and increased fetal liver volumes have been measured in IUGR and in insulin-dependent diabetes mellitus (IDDM) pregnancies, respectively.\(^{8}\)

The blood supply to the fetal liver has been evaluated by color Doppler ultrasound as shown in Figure 9, that presents the distribution of umbilical blood flow to the ductus venosus and to the liver with increasing gestation.\(^{63}\) The percentage of umbilical blood flow shunted through the ductus venosus decreases significantly (from 40%-15%); consequently, the percentage of flow to the liver increases. The right lobe flow changes from...
20% to 45%, whereas the left lobe flow is approximately constant (40%). These changes are related to different patterns of growth of the umbilical veins and ductus venosus diameters and support the hypothesis that the ductus venosus plays a less important role in shunting well-oxygenated blood to the brain and myocardium in late normal pregnancy than in early gestation, which leads to increased fetal liver perfusion. However, when growth restriction occurs, after the initial stage of adaptation, ductus venosus shunting is increased, representing an intermediate stage before failure.9 In more severe IUGR, the percentage of umbilical blood flow shunted through the ductus venosus is greater than the 90th percentile of control fetuses. This is accomplished with a concomitant reduction in the percentage of blood flow to the right lobe of the liver, with evidence of reversed blood flow from the right lobe and portal system into the ductus venosus evaluated both by volume blood flow calculations and by direct pulsed Doppler waveform direction.9 These changes provide therefore a relatively constant blood flow to the heart and brain at the expense of fetal hepatic perfusion.

Supporting these data, the normal fetal brain/liver volume ratio shows a significant reduction with gestational age, and is significantly higher in growth restricted fetuses, with a significant inverse relationship between functional age, and is significantly higher in growth restricted fetuses. With an intermediate stage before failure.9 In more severe IUGR, the percentage of umbilical blood flow shunted through the ductus venosus is greater than the 90th percentile of control fetuses. This is accomplished with a concomitant reduction in the percentage of blood flow to the right lobe of the liver, with evidence of reversed blood flow from the right lobe and portal system into the ductus venosus evaluated both by volume blood flow calculations and by direct pulsed Doppler waveform direction.9 These changes provide therefore a relatively constant blood flow to the heart and brain at the expense of fetal hepatic perfusion.

Conclusions

In these 50 years, we have known the human fetus as a healthy person with a big brain. It will be very important in the future to complete our knowledge about morphologic and functional development of single fetal organs: we know something but much more is needed.

The placenta is a fetal organ that plays a key role: it regulates fetal growth and development. Therefore, many fetal diseases originate much earlier in the placenta, and only later develop in the fetus. It is very important that every fetal disease has a staging, an evaluation of degree of severity. The expression “fetal distress” should no longer be used as such because it is a big basket, a container of different disease entities.

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