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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." Medicine

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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.[1] 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.[1]

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.[1] 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.[1] 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[2] 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[2] 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[3] 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).[3] Later on, Battaglia and Meschia[4] 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 uteroplacental O_2 use.[4] 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.[5-9] We then estimated umbilical oxygen uptake as the product of umbilical blood flow and umbilical O_2 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[3] 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