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Is it time to reconsider fetal growth charts?

Abstract

Early detection of fetuses with abnormal weight, either with intrauterine growth restriction or macrosomia is very important, considering the additional risks and comorbidities that these fetuses are exposed to. In every population there are external factors that can interfere with normal fetal growth, therefore, the fetal growth charts should be revised in order to timely identify and manage cases of abnormal fetal weight. We must also consider the epigenetic factors influencing fetal growth patterns, and the fact that for a longer time period the normal fetal birth weight will modify, hence the need for periodic review of fetal growth curves.

Keywords: *fetal growth, growth chart, birth weight, insulin-like growth factor*

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Introduction

As ultrasound investigations in pregnancy became available, physicians could follow every stage of fetal growth, while estimating fetal weight. This issue is of major importance in terms of increasing the quality of medical care and the opportunity to identify before birth fetuses with structural abnormalities and fetuses with abnormal patterns of growth and development. Using standard criteria, these fetuses are classified in fetuses with low birth weight, large for gestational age fetuses (LGA) and small for gestational age (SGA) fetuses. The main reason for developing a fetal weight chart based on Romanian population is the ability to identify fetuses with abnormal growth patterns (i.e. fetuses SGA, fetuses LGA) with greater accuracy, given the increased mortality and morbidity in these cases.

Pregnancy has a duration of 280 days calculating from the first day of the last menstrual period (gestational age is calculated in weeks of amenorrhea) or 266 days after fertilization (in this case we calculate the embryonic age). Given the fact that the moment at which the fertilization may occur can be delayed by up to 5 or 6 days after the intercourse, pregnancy dating by this method is not very accurate. Therefore, the great majority of obstetricians use the last menstrual period for pregnancy dating.

Pregnancy can be divided into two distinct periods if we refer only to the growth and development of the conceptus. The first period is the embryonic period, from the third week of amenorrhea, up to 11 weeks of amenorrhea. In this stage, the development and differentiation of tissues and organs begins, resulting embryo formation (organogenesis). The second period, which extends from 11 weeks of amenorrhea (or 8 weeks after the moment of fertilization) until birth, is the phase of fetal growth (the product of conception is called a fetus), a stage in which the fetus grows in size and weight, reaching about 50 cm in the near term and 3200-3400 grams[1].

The placenta and fetal growth

Fetal birth weight varies greatly and is influenced by maternal, fetal, constitutional, genetic, nutritional and environmental factors. Fetal growth and development largely depends on the placenta, the organ responsible for nutrients and gas exchange between the mother and the fetus.

The most important structure in the human reproductive system is the placenta. Its originates in the trophoblast, the embryonic cell layer that begins to develop in the embryonic stage of morula. The embryo will be surrounded by the trophoblast cells, that are responsible for invasiveness required for the implantation process. These cells will be involved in the fetal nutrition and gas exchange between the mother and the fetus, but also in the endocrine function of the placenta[2].

In the second week after fertilization, the trophoblast begins to differentiate into cytotrophoblast located near the conceptus, and syncytiotrophoblast, located near the decidua. The cytotrophoblast is a cellular layer with single nucleated cells, delineated by a membrane, that will differentiate in the syncytiotrophoblast (i.e. acellular layer, agglomeration of nuclei of various shapes and sizes, located in a cytoplasmic mass). The syncytiotrophoblast is involved only in the materno-fetal nutrient exchange process while thecytotrophoblast cells have a secretory function[2].

The placenta is responsible for fetal growth and development through the nutrient exchange process between the mother and the fetus, but it also has an endocrine function, supplying the hormones needed for the fetal growth process.

The growing fetus depends on the nutrients and metabolite exchange from the mother's body through the placenta. However, the fetus may alter the parameters of the intrauterine environment, as well as its own process of growth and development by hormone secretion[3].

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In pregnancy, the placenta is involved in synthesis and secretion of a large number of steroid hormones (i.e. progesterone and estrogen), protein hormones (i.e. gonadotropin releasing hormone, corticotropin releasing hormone, thyrotropin-releasing hormone, somatostatin, human chorionic gonadotropin, human chorionic somato-mammotropin, human chorionicthyrotropin, human chorionic adrenocorticotropin, growth hormone, growth hormonereleasing hormone, alpha-fetoprotein, relaxin, prolactin, cytokines and growth factors, inhibin, activin, follistatin, opiates, atrial natriuretic peptide), thromboxanes and prostaglandins.

Insulin like grwoth factor

Insulin-like growth factors, IGF-I and IGF-II, are peptidic molecules consisting of a single chain of amino acids, involved in growth process both in the fetal period and after birth. These molecules bind to specific receptors (IGF1R and IGF2R), insulin receptor (InsR) and a hybrid receptor: IGF1R-InsR[3].

According to Hellström and contributors[4], the most important factors that stimulate fetal growth are IGF-I and insulin, and to a much lesser extent, the growth hormone. For example, children with genetic abnormalities that interfere with the synthesis of growth hormone (i.e. low levels of growth hormone or growth hormone resistance syndromes) have a normal birth weight, but as they grow, the delayed development and small weight will occur. Fetal serum IGF-I levels measured in utero in the second and third trimesters of pregnancy correlates with fetal weight. The highest values of fetal serum IGF-I were recorded towards the end of the third trimester, being known the fact that the development of the fetal adipose tissue and the fastest growing rate in fetal weight is achieved during this period. IGF-I concentrations measured in umbilical cord showed values similar to those in fetal serum, and are significantly lower in preterm infants and fetuses with intrauterine growth restriction than in normal weight newborns[4].

In a study on correlations between umbilical cord levels of IGF I and fetal birth weight, Yang&Yu[5] showed that the fetal serum levels of IGF-I, Insulin-like growth factor-binding protein (IGFBP)-3 and maternal factors have more influence on fetal birth weight than insulin or growth hormone. The study was conducted on samples of blood taken from the umbilical cord at birth, and the newborns were divided into three groups based on the birth weight - normal birth weight, SGA and LGA. Premature newborn were included in the study; newborns LGA from mothers with gestational diabetes were excluded. Serum levels of insulin, growth hormone, IGF-I and IGFBP-3 were measured. Serum levels of IGF-I and IGFBP-3 were lower for preterm babies than for term babies. There were no significant differences between growth hormone and insulin levels. In addition, serum levels of IGF-I and IGFBP-3 increased with gestational age, which correlates with fast fetal weight gain during the last trimester of pregnancy. Fetal insulin and growth hormone have a smaller influence on fetal growth and development than fetal IGF-I, as these hormones do not correlate with fetal birth weight. Transplacentar glucose transfer and insulin are essential in the production of fetal IGF-I[5].

Fetal metabolic programming

An important element to be considered is represented by epigenetic factors and their influence on fetal development. These factors may change the phenotype of an organism without inducing changes in the genes. Epigenetic factors can modify the way in which genetic information is translated by activating certain genes and by inactivating others in protein synthesis. These epigenetic changes can sometimes be inherited from one generation to another. The most frequent epigenetic changes are deoxyribonucleic acid methylation and chromatin remodeling through histone modification. In an animal study model using Wistar rats, maternal obesity lead to offspring organogenesis anomalies and metabolic dysfunction, proving the fact that overnutrition could modify fetal metabolic programming[6,7]. In 2013, Sookoian et al. presented some very interesting hypotheses about the influence of environmental factors, in the development of certain diseases in adulthood[8]. Impaired fetal growth in utero is often associated with serious conditions in adulthood such as hypertension, coronary heart disease, insulin resistance, and type 2 diabetes. Inadequate nutritional intake during intrauterine development, can interfere with fetal metabolic programming by modulating the fetal switch of histone acetylation -deacetylation, changes in stem cells, changes in cell differentiation, changes in cytosine residues. The link between fetal weight and conditions experienced in adulthood was originally made for SGA fetuses subsequently being described in the case of large fetuses. Patho-physiological explanation of this phenomenon is modifying fetal metabolism in response to the nutritionally inadequate intrauterine environment. Using computational molecular biology and a computer program that is able to render possible interactions and links between genes and the proteins they encode, Sookoian and contributors investigated possible connections between genes and proteins that may influence fetal weight through fetal metabolic programming[8]. The results rendered by this bio-informatics platform, about possible connections between genes, proteins and regulatory mechanisms showed that a fetus found in an unsuitable environment from a nutritional perspective, may present changes in gene expression, affecting differentiation of pluripotent stem cells, of histone acetylation- deacetylations witch, elements that can cause certain diseases in adulthood[9].

Conclusions

Intrauterine fetal growth and development depends on maternal, fetal and environmental factors. Every child has an ideal growth pattern that could be achieved at birth depending on the evolution of pregnancy,

the presence of comorbidities and other factors. There is no consensus regarding the method used for fetal growth evaluation. There are studies that support the use of customized standards, with parameters that can be modified depending on the particularities of each case, while other studies conclude that population-based fetal growth standards allow better detection of fetuses with abnormal growth. ■

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