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# Placenta and Fetal Growth Restriction: a Review

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**ABSTRACT**

**Introduction:** the gestational process is composed of several closely related stages that are progressive, including placentation. Changes during placental development are considered important, as they can compromise the adequate nutrition of the fetus, and the lack of fetal nutrition can lead to pregnancy interruption as well as fetal growth restriction. Fetal growth restriction occurs when the fetus does not reach the expected size or determined by its genetic potential, being clinically identified when the fetal weight is below the 10th percentile for gestational age. The histopathological findings related to Fetal Growth Restriction are very varied, with no specific characteristics for this condition. This can be explained by the fact that RCF has a heterogeneous cause and late or early onset. This review contains information about the placenta, fetal growth restriction and the most common changes in placentas from pregnancy with fetal growth restriction.

**Keywords:** Pregnancy; Placenta and Fetal Growth Restriction.

## Introduction

Intrauterine growth restriction, also known as fetal growth restriction, occurs when the fetus does not reach the expected size or determined by its genetic potential, clinically identified when fetal weight is below the 10$^{th}$ percentile for gestational age[17].

Pregnancies with fetal growth restriction are classified as high risk. Defined as the one in which the health of the mother and/or fetus and/or newborn is more likely to be affected when compared to the population mean[1].

Pregnancy is a complex process where changes occur in the uterine environment in order to provide favorable conditions for the development of the embryo[3]. The gestational process is composed of several closely related stages that are progressive, among them is placentation[5].

The placenta is a transient fetal-maternal organ composed of two portions, one maternal, derived from the endometrium, and one fetal, derived from the chorionic tissue, these need to interact with each other satisfactorily for the healthy development of pregnancy[2]. It has immunological function, gas and nutrient exchange and hormone production enabling the maintenance of pregnancy[18].

The placenta has adaptive responses to various damage, such as chronic hypoxia and oxidative stress, and that may appear in a non-homogeneous manner through placental territory. Placental architecture changes in various maternal and fetal pathologies[15].

This review searched the literature for information about the placenta, fetal growth restriction and the most common changes in placentas from pregnancy with fetal growth restriction. It was structured based on articles obtained from the databases: SCIELO, LILACS, MEDLINE, BVS - Biblioteca Vitual em Saúde e GOOGLE SCHOLAR, during the months of february and march of the year 2022.

### The Placenta

Physiologically, the placenta can be defined as the extracorporeal organ that interacts with the endometrium to nourish and protect the fetus and that orchestrates maternal adaptations to pregnancy[2].

The human placenta develops soon after nesting, the trophoblast begins to proliferate rapidly, and gradually differentiates into two layers one internal cytotrophoblast, a layer of mitotically active mononuclear cells that form new cells that migrate into the growing mass of syncytiotrophoblast where they fuse and lose their cell membranes; and an outer syncytiotrophoblast formed by a multinucleated protoplasmic mass, in which no cell boundaries can be observed[11].

With the implantation of the blastocyst in the endometrium, it undergoes a transformation known as the decidual reaction, where the endometrial cells change, increasing in size and accumulating in their interior glycogen and lipids that will be a source of nutrition for the embryo[18].

At the beginning of the second week of embryonic development, as the amnion, embryonic disc and primitive yolk sac form, isolated cavities appear - the gaps in the syncytiotrophoblast. These gaps

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soon become filled with a mixture of maternal blood from ruptured endometrial capillaries and eroded uterine gland cells. The fluid in the lacunar spaces - the embryotroph - passes through diffusion to the embryonic disc and provides nutritive material to the embryo, characterizing the beginning of the uteroplacental circulation[18].

The layer of cells located below the syncytiotrophoblast, the cytotrophoblast, proliferates and invaginates towards the cytotrophoblast forming the primary villus, characterized by a cytotrophoblastic nucleus and an outer layer of syncytiotrophoblast. Around the 17th–18th day of development, the extraembryonic mesoderm penetrates the villus, forming the secondary villus, composed of mesoderm surrounded by cytotrophoblast and an outer layer of syncytiotrophoblast. The end of the third week of embryonic development is marked by the differentiation of mesenchymal cells providing the appearance of capillaries within the villous nucleus, which characterizes the tertiary villi[21].

The erosive syncytiotrophoblast invades the endometrial connective tissue and the blastocyst slowly penetrates the endometrium. The syncytiotrophoblastic cells displace endometrial cells in the central part of the implantation site. Endometrial cells undergo programmed cell death, which facilitates invasion. The molecular mechanism of implantation involves synchronization between the invading blastocyst and a recipient endometrium[10].

**Fetal Growth Restriction (FGR)**

Changes during placental development are considered important, as they can compromise the adequate nutrition of the fetus, and the lack of fetal nutrition can lead to pregnancy interruption as well as fetal growth restriction[17].

The definition of small for gestational age newborns as those with an estimated weight below the 10th percentile, includes in a risk group fetuses that do not present any complications or sequelae, common to fetuses with growth restriction, being said to be constitutionally smaller, that is, it has a growth curve parallel to the normal growth curve[19].

Fetal development is marked by phases of cellular hyperplasia and hypertrophy that occur at different times during pregnancy. When FGR occurs early, that is, in the cellular hyperplasia phase, symmetrical fetuses are present, unlike when FGR occurs in the cellular hypertrophy phase, which results in the presence of asymmetrical fetuses. The presence of early FGR is usually associated with drug use, genetic alterations and fetal infections, it has a high lethality and the possibility of medical management is restricted, but late installed FGR is related to placental insufficiency, being, therefore, linked to preeclampsia enabling medical intervention in order to reduce morbidity[19].

Ultrasonography is an important tool for the diagnosis of FGR, since the estimate of fetal weight must be performed taking into account the biometric measurements of the fetus, such as abdominal circumference, biparietal diameter and femur measurement, as the association of this information decreases. the standard deviation of the fetal weight calculation. That is, the fetal weight analyzed alone adds little information to the ultrasound diagnosis of fetal growth restriction[8].

Currently, the use of Doppler in the assessment of uteroplacental circulation has been used as a tool for the diagnosis of FGR. This preference is explained by the fact that the hemodynamic alterations present in fetuses with FGR occur earlier when compared to the biometric alterations[8].

The etiology of fetal growth restriction is complex, it may be related to maternal, fetal, placental factors as well as the association of more than one fator[12]. The treatment for fetal growth restriction during pregnancy, that is, intrauterine, is limited, but the diagnosis during prenatal care is extremely important, since, when the diagnosis fails during the gestational period, the fetus presents a risk four times higher adverse outcomes compared to those diagnosed during pregnancy[19].

Restricted fetal growth is one of the leading causes of perinatal morbidity and mortality, second only to preterm birth. Low birth weight can have a lifelong consequence, studies show that FGR can increase vulnerability to chronic diseases in adults[17]

The restriction of nutrient supply experienced by the fetus during FGR can lead to a phenomenon known as developmental programming, first mentioned in the literature by Barker and his team in the 1980s. The lack of nutrients promotes an endocrine and metabolic adaptation of the fetal organism in order to survive the period of nutritional stress, but after birth and the normalization of food supply, this adaptation will result, in the long term, in diseases such as diabetes and obesity[4].

Maternal malnutrition during pregnancy has contributed negatively to fetoplacental development. In developing countries, maternal malnutrition has an incidence greater than 10% and has a significant proportion in industrialized IUGR (intrauterine growth retardation) countries[6].

Some causes and risk factors for fetal growth deficit related to maternal pathologies are: age, nutritional status, health problem such as hypertension, chronic kidney disease, diabetes, use of illicit drugs, tobacco, previous child born with IUGR, exposure to toxics, residence in high attitudes, race, ethnicity, infertility, parity and anemia[17].

Maternal nutrition is shown as a factor that is closely related to fetal growth, with malnutrition being an important cause of fetal growth retardation worldwide[14].

Anemia is one of the factors associated with nutritional deficiencies, which occurs more frequently during pregnancy, due to an insufficient maternal intake or a low in the mother's nutrient reserve, providing the compromise of the mother-fetus binomial, and due to this failure in the food intake may lead to a link between anemia and IUGR[13].

Pregnant women with poorly controlled diabetes mellitus who have vascular changes is also one of the likely factors that causes fetal growth deviations, as the placenta of these pregnant women with diabetes has a high size, larger than normal, presenting structural changes that make it difficult to pass of nutrients needed by the fetus[19].

**Placental Changes Related to Fetal Growth Restriction**

The presence of morphological changes in placentas originated from complicated pregnancies is common, but when fetal growth restriction occurs at the end of pregnancy, there is a lower probability of morphological changes in the placenta when compared to early-onset FGR[16].

There is already knowledge of the main placental histological changes present in the pathology of FGR. However, it is important to note that about 25% of placentas from pregnancies with fetal growth restriction do not show any morphological abnormality on routine macroscopic and histological examination. Among the most common alterations we can mention: syncytiotrophoblastic nodes, excess cytotrophoblastic cells, thickening of the trophoblastic basement membrane, villous fibrosis, reduced villus volume, reduced intervillous space and nonspecific inflammatory lesions[16].

The histopathological findings related to Fetal Growth Restriction are very varied, with no specific characteristics for this condition. This can be explained by the fact that FGR has a heterogeneous cause and late or early onset. The changes are mainly associated with clinical and histological features of impaired maternal uteroplacental perfusion secondary to defective extravillous trophoblast invasion and its consequences[16].

Factors in fetal development delay may be related to placental causes, including: abnormal placental implantation, altered structure of the same, such as the single umbilical artery, placenta previa, uterine abnormalities, circumvallate placenta, chorioangioma, placental mosaic and placental infarctions[9].

Placental insufficiency is the most common cause of IUGR, causing fetal hypoxemia, therefore impairing fetal renal perfusion, with poor redistribution in the fetal circulation, where there is a reduction in amniotic fluid, which may lead to oligohydramnios[22].

The placental causes of IUGR will cause uteroplacental vascular insufficiency, causing a deficit in the transfer of nutrients from the mother to the fetus, due to the reduction in flow and perfusion pressure, increasing the vascular placental resistance and thus the exchanges by the vascular surface of deficient form[20].

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## Mini Curriculum and Author's Contribution

1. Danyella Santana da Costa – Pharmaceutical; MsC student. Contribution: Effective scientific and intellectual participation for the study. Bibliographic research. Elaboration and draft of the manuscript. Critical review and final approval.

2. Marcos Aurelio Santos da Costa – MsC; PhD student. Contribution: Effective scientific and intellectual participation for the study. Critical review of the manuscript.

3. Renatha Claudia Barros Sobreira – MsC; PhD student. Contribution: Effective scientific and intellectual participation for the study. Critical review of the manuscript.

4. Fernanda das Chagas Ângelo Mendes Tenório – PhD. Contribution: Guiding professor. Critical review and final approval.

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