Etiopathogeny

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Introduction

Fetal growth restriction (FGR) refers to a poor growth of the fetus while inside the mother's womb during gestation and is to be distinguished from *small for gestational age* (SGA) fetuses. FGR is defined as a birth weight less than the 10th percentile [1]: the fetus has not reached its genetic determined growth potential at a given gestational age due to one or more causative factors. In contrast to this, the SGA fetus has reached its growth potential, and there is no pathology causing the poor growth. This fetus grows with a constant velocity, parallel to a specific percentile through the pregnancy. A normal postnatal outcome is to be expected. Differentiation can be very difficult, and umbilical artery Doppler can be useful to differentiate the constitutionally small fetus from the pathologically small fetus [2–6].

Since birth weight is a strong predictor of pregnancy outcomes, it is important to identify the causes of FGR, which can be divided into fetal, maternal, and placental causes. Regulation of fetal growth is multifactorial and complex. It is known that fetal weight is directly associated with placental size. Placental insufficiency is associated with most cases of FGR. There are many causes not primarily caused by placental insufficiency but indirectly leading to it [7]. So placental and maternal causes for FGR have a common final pathway of decreased placental perfusion and transfer of nutrients to the fetus. Fetal-induced FGR is caused secondarily through genetic or infectious diseases.

Until 20 weeks of gestational age, fetal growth is characterized by hyperplasia, which means through growth of the number of cells. Later on, fetal growth is primarily characterized by hypertrophy, the growth of existing cells [4]. FGR in the first half of pregnancy is caused especially by intrinsic factors like chromosomal

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L. M. M. Nardozza et al. (eds.), *Fetal Growth Restriction*,
https://doi.org/10.1007/978-3-030-00051-6_3

aberration or infections, whereas FGR in the second half of pregnancy is primarily caused by extrinsic factors that lead to placental insufficiency. If FGR is caused by intrinsic factors, FGR is symmetric. Extrinsic factors cause asymmetric FGR. In these cases, there is an increase in the head circumference to the abdominal circumferences, the so-called brain sparing.

Fetal Causes

Fetal causes are numerous and range from genetic and structural malformations to infective diseases. Genetic diseases lead to 5–20% of causes of FGR [7]. Trisomies are often associated with fetal growth restriction, which is more severe with trisomy 18 than trisomies 13 and 21 [5, 6]. FGR is also associated with trisomy 16 as well as with Wolf-Hirschhorn syndrome (4q deletion) and Cri du chat syndrome (5q deletion). Also to be taken into consideration is monosomy X, also known as Turner syndrome. Triploidy and an extra set of chromosomes are also highly linked to fetal growth restriction. Since incidence of FGR is high in fetuses with genetic abnormalities, an amniocentesis or placental biopsy should be considered in cases of unexplained and early occurring FGR.

Congenital malformations without genetic cause are responsible for 1–2% of FGR. This includes malformations like congenital heart disease, diaphragmatic hernia, omphalocele, gastroschisis, and anencephaly [6, 8].

Infections during gestation are important to mention when talking about causes for FGR. In fact they make up to 10% of the cases. The TORCH (toxoplasmosis, other (syphilis), rubella, cytomegalovirus, and HIV) organisms are considered the leading organisms causing FGR. In developed countries toxoplasmosis and cytomegalovirus are considered the most important infections and should be therefore tested in pregnancy in order to control costs [9]. There is no evidence for testing all TORCH organisms also considering rising costs. However it should be taken into consideration that malaria is the most common cause of FGR worldwide [10, 11]. Single umbilical artery is also considered as a cause for FGR.

Multiple gestations are also associated with FGR and make 3% of the cases. Twin pregnancies should be under constant control. After 28 weeks of gestation, growth rate decreases. FGR of one fetus could indicate genetic abnormalities or infections of the fetus or be a hint for twin-to-twin transfusion syndrome [12, 13].

Maternal Causes

Size at birth depends on numerous factors including race, sex, parity, maternal weight, and height [14, 15]. Fetal nutrition depends on the ability of the mother to provide oxygenated blood. Maternal causes of FGR are usually related to placental insufficiency, the main reason for FGR that can concern up to 3% of all pregnancies. Pathogenesis is not totally clear yet, but it seems that defects in placental circulation and transport affect nutrient transport to the fetus and therefore lead to FGR.

Placental insufficiency and FGR are risk factors for stillbirth. In fact up to 43% of stillborn are FGR fetuses [16]. Placental insufficiency is not a specific placental disease, in fact there a numerous factors leading to it. Abnormal fetal genome as well as chronic infection and many maternal diseases can affect placental tissue and therefore cause FGR. To conclude decreased uteroplacental blood flow, reduced blood volume, and reduced oxygen transport capacity are responsible for placental insufficiency [17].

Decreasing fetal perfusion leads to hypoxia and therefore to FGR. Chronic hypertension, preeclampsia, pregestational diabetes, chronic renal insufficiency, systemic lupus erythematodes, and antiphospholipid syndrome affect fetal microcirculation. This causes decreasing fetal perfusion. Chronic hypertension, whether isolated or in the form of preeclampsia, is the most important maternal factor influencing fetal growth: severe, pregnancy-induced hypertension reduces birth weight by approximately 10%. A history of prior low-birth-weight infants is responsible for the same amount of reduction in birth weight. Interestingly, a preexisting, uncomplicated maternal hypertension does not reduce fetal growth.

In addition to maternal disorders, also poor nutrition status, substance abuse, and pharmacotherapy affect fetal growth and can lead to FGR. Women with lower socioeconomic status as well as women living in developing countries are at higher risk of a poor nutrition status but also of maternal anemia, poor prenatal care, and substance abuse problems. Smoking during gestation, especially smoking of more than 15 cigarettes per day, is highly associated with a lower birth weight and associated with reduced oxygen transport capacity. Important to mention is that especially smoking in the third trimester of the pregnancy leads to FGR [18, 19]. If pregnant women quit smoking until 16 weeks of gestation, birth weight does not differ from women who never smoked before [20]. Therefore women should be motivated to quit smoking in early pregnancy. Women living in high altitudes are also at risk of FGR, also because of reduced oxygen transport capacity.

Placental Causes

Placental causes for IUGR are placental abruption, maternal floor infarct, placental mosaicism, velamentous cord insertion, as well as placenta accreta [7, 17, 21]. Genetic and environmental factors can influence early placental development including poor placental growth, inadequate trophoblast invasion, and altered immuno-regulatory environment. These processes in turn can trigger altered nutrient delivery, hypoxic response, and/or a variety of inflammatory responses that are linked to adverse perinatal outcomes.

Placental-Mediated Complications

There are multiple obstetrical concerns for which placental biomarkers can have beneficial clinical applications. Early prediction of poor fetal growth, premature delivery, and maternal preeclampsia (PE) is important, as careful monitoring and

interventions can improve outcomes and save the lives of babies and mothers. However, these are heterogeneous conditions for which a variety of genetic and environmental influences (e.g., maternal obesity, diabetes, low socioeconomic status, and poor nutrition) can contribute to risk. Defining abnormal placental health is also challenging as, even in normal pregnancies, there is extensive within and between placenta variation in terms of gross pathology and molecular changes [22]. Recently, protein and nucleic acid biomarkers have been identified by modern genomic technologies which have been discussed to be related to placental and fetal health outcomes. In the future it is expected that incorporation of a combination of biomarkers along with clinical maternal and fetal parameters will serve to a better understanding of placental pathology and would optimize risk assessment.

Conclusion

The ethiopathogeny of intrauterine growth restriction is diverse. Besides well-established maternal, extrinsic, and intrinsic causes, recent improvements in genomic technologies and increase in knowledge have directed the interest toward biomarkers in investigating placental and fetal status. A combination of clinical data along with new results from biomarkers is probably the way to go forward in diagnosing and surveilling the fetus at risk for fetal growth restriction in the future.

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