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Review

FETAL GROWTH RESTRICTION: A GROWTH PATTERN WITH FETAL, NEONATAL AND LONG-TERM CONSEQUENCES.

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ABSTRACT

Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) are the terms used for a fetus which has not attained its full growth potential for gestational age. FGR is a multifactorial syndrome responsible for increased fetal and neonatal morbidity and mortality as well as long term adverse outcomes involving auxological, metabolic, organic and functional domains. Clinicians distinguish early and late onset FGR, in relation to specific fetal anthropometric parameters related to the possible primary etiology and to different patterns of placental and maternal cardiovascular pathologies. Delivery of an early onset FGR or growth impaired newborn with congenital pathology should be in tertiary care center, given the high perinatal morbidity. At hospital discharge the FGR infant should be enrolled, in a multidimensional individualized developmental follow-up. Subjects who have suffered from FGR should adopt a healthy lifestyle.

1. Introduction

Fetal growth restriction (FGR), or Intrauterine Growth Restriction (IUGR), refers to poor growth of a fetus during pregnancy.
FGR frequency will vary depending on the different discrimination criteria adopted. It should be extremely important to use local or national fetal growth graphs in order to avoid some confounding factors (1).
Perinatal complications of FGR are frequent and at least 60% of the 4 million neonatal deaths, occurring worldwide every year, are associated with low birth weight, caused by FGR, preterm delivery, and genetic abnormalities (2).

2. Fetal growth determinants and assessment of Fetal Growth Restriction

Human fetal growth is the result of the interaction of the individual genetic growth potential and its modulation by the health status of the fetus, placenta, and mother. Maternal genes influence birth weight more than paternal genes, but whole genetic factors account for 30 to 50 percent of the variation in birth weight, with the remainder due to environmental factors (3).

Recent research conducted on MZ and DZ twin pairs, useful for differentiating the relative influences, showed that shared environmental factors are prevalent on genetic ones (4).
In clinical practice as well as in some scientific literature the two terms FGR and SGA are still frequently used synonymously, but substantial differences exist between them. A newborn is defined adequate for gestational age (AGA), if birth weight is between the 10^{th} and the 90^{th} percentile for a specific ethnicity and gender, while the term SGA is used for a newborn whose birth weight is less than the 10^{th} percentile. Some fetuses with a slowing down of their growth trajectory, at birth do not fall below the 10^{th} centile, and this situation could lead to an underestimation of a cohort of patients that are at higher risk of neonatal complications (5).
Obstetricians routinely assess prenatal growth by fetal ultrasonography. Fetal biometric measurements are the rate of change in biparietal diameter, head circumference, femur length, and abdominal circumference, characterized by specific peaks during gestation. Fetal weight, the most important parameter, shows a velocity peaks at around 35 weeks gestation with substantial difference between singletons and twins (6).
FGR, although there is not still a shared definition (5), defines a fetus that, based on sonographic estimated fetal weight and abdominal circumference measurement, does not reach at birth the estimated target weight for

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gestational age (GA), thus showing a progressive reduction in fetal growth centiles.

Generally, obstetricians define a small fetus when the ultrasonographic estimated fetal weight is below the 10th percentile for gestational age in the second half of pregnancy. But this anthropometric definition has actually been adopted from a neonatological context of analysis (7). Moreover, while neonatologists can often rely, at least for singletons, on well standardized neonatal birth weight percentiles, for obstetricians is still controversial which standard of fetal growth should be used (8). The use of customized fetal growth charts has been proposed for more appropriate identification of fetal growth restriction considering anthropomorphic variables of the mother and fetus both for singletons (9), and more recently for twins (10). The use of a percentile to define FGR is problematic because it does not allow the obstetricians to distinguish among fetuses who are constitutionally small versus those who are small because of a pathological process that impede them from achieving their genetic growth potential. Indeed, it has been demonstrated that about 70 percent of fetuses who are estimated to weigh below the 10th percentile for gestational age are small in relation only to constitutional factors such as maternal ethnicity, parity, or body mass index (11). These constitutionally small fetuses are not at risk for perinatal complications. On the other hand, it can occur that a malnourished fetus whose estimated weight is slightly greater than the 10th percentile may be misclassified as appropriately grown and at low risk of adverse perinatal outcome, even though its weight may be far below its genetic potential. Recently a survey of expert suggested that growth restriction in the newborn should be identified as one of the following conditions; a birth weight less than the 3th percentile, or when three of the following are met: Birth weight <10th percentile, Head circumference <10th percentile and Length <10th percentile. A moderate FGR is defined as birth weight in the 3th to 10th percentile, and severe FGR as less than the 3th percentile (12).

3. Epidemiology

The incidence FGR varies among populations, also in relation to concomitant prematurity rate (from 7 to 13%), being both more prevalent in resource-limited countries. A still frequent interchangeability of the terms FGR and SGA contribute to the difficult interpretation of some studies, that may include both categories of infants and consider as FGR also newborn that are constitutionally normally small (13). Thus, most of neonatal studies used the term SGA, confusing the two terms. Considering the SGA newborn (< 10th percentile), the birth incidence is approximately 10 percent of term infants in developed countries, compared with 20 percent of term infants in developing countries (14). An increased neonatal death (almost 22%) has also been described in infants born SGA (13).

4. Etiology

Fetal, placental, maternal factors may be responsible for FGR are listed in Table 1. In newborns with an identified underlying cause a fetal environmental condition is present in two-thirds and a genetic disease or malformation in 1/3 of cases (15). Genetic diseases are often responsible for preterm birth and FGR, leading to a substantial increase in neonatal care intensity (16, 17).

With the advance of molecular biology, researchers have identified several maternal, placental and fetal genes with metabolic and endocrine effect involved in FGR (18).

The identification of a potential cause of FGR, requires a specific and individualized prenatal surveillance as well as the choice of a specialized center for obstetric management of the high-risk delivery along with the availability of a fully equipped neonatal intensive care unit.

Determinants for FGR	
Maternal age, body composition, fertility and environmental conditions	Extremes of maternal age (< 16 and > 35 years), Maternal pre-pregnancy height and weight (BMI less than 20, weight less than 45 kg and more than 75 kg) assisted reproductive technics, maternal prolonged high-altitude residence during pregnancy
Substance abuse in pregnancy	Alcohol, cigarettes, heroin, cocaine
Maternal pathologies	Pregestational diabetes mellitus, cyanotic heart disease chronic pulmonary disease, chronic kidney disease, hypertension, malabsorption, LES, severe chronic anemia, maternal poor nutritional status, poor medical care
Teratogens exposure	X radiation, valproic acid, warfarin, antineoplastic agents, folic acid antagonists
Chromosomal mosaicism affecting the placenta.	Severity of FGR is related to chromosomes involved, proportion of mosaic cells and eventual uniparental disomy
Placental anomalies and uterine malformations	Single umbilical artery, velamentous umbilical cord insertion, other placental anomalies
Multiple pregnancies	Related to the number of fetuses and chorionicity
Placental ischemic diseases	Preeclampsia, abruptio placenta
Fetal genetic pathologies	Aneuploidy, single gene mutations, copy number variations, aberrant genomic imprinting, genetic syndromes
Fetal malformations	Cardiac, CNS, Gastrointestinal, and related to both the type and number of anomalies
Fetal infections	CMV, Toxoplasma, rubella, varicella zoster, herpes simplex, syphilis

Table 1. Main congenital, acquired and environmental conditions related to FGR

5. Intrauterine growth in multiple pregnancies

In the last years, in western countries we assist to an increase in average maternal age, defined as being more than 35 years old, as well as paternal age, considered advanced in case of more than 40 years old. The total fertility rate has been steadily falling too, thus one in six couples is infertile. Thus, about 10% of them need help of assisted reproductive technology (ART). These conditions along with an impelling social pressure are frequently a source of psychological suffering within the couple (19).

Advanced parental age and the diffusion of ART, led to a significant increase of multiple births (20), so that today approximately 3 percent of live births are twins (21). Two different types of twins are identified; monozygotic or identical (MZ) and dizygotic or non-identical (DZ). MZ twins develop when one egg is fertilized by a single sperm and during the first two weeks after conception, the developing embryo splits into two. As a result, two, generally considered genetically identical babies develop. DZ twins occur when two eggs are released at a single ovulation and are fertilized by two different sperm.

These two fertilized eggs then implant independently in the uterus. DZ twins share the same type of genetic relationship as non-twin siblings.

Although MZ twins sharing the majority of their genetic makeup are generally considered identical, differences at the epigenetic level are responsible for phenotypic discordance for a wide range of traits (22, 23).

Opposite sex twin pairs, accounting for about 1/3 of all twin births, are DZ. In case of same-sex twin pairs zygosity determination can be done by a DNA test. Nevertheless, a possible diagnosis can be made at birth based on an examination of the placenta and fetal membranes. The twin pair is considered MZ if there is only one placenta and DZ, when each twin has its own placenta, outer membrane (chorion), and inner membrane (amnion). This is also the case for one-third of MZ pairs, therefore, the appearance of two of placentas and two sets of membranes does not enable a definitive assessment to be made regarding twin type. MZ twins can be categorized into four types based on when the division of the embryo occurs. If the cleavage happens before the 6^{th} day after conception, there will be two placentas, two chorions, and two amnions. When it takes place between the 6^{th} and 10^{th} day after conception, there will be one placenta, one chorion, and two amnions. This is the most frequent type accounting for about 64% of MZ twins. If the embryo splits between the 10^{th} and the 14^{th} day, the result will be twins sharing the one placenta, one chorion, and one amnion. This type is less common, accounting for 4% of MZ twins. If cleavage of the embryo occurs after the 14^{th} day, there is an increased risk that the division will be incomplete leading to conjoined twins.

At birth it can be sometimes difficult to identify the two separate placentas, and parts of membranes can be implanted so closely together in the womb that the individual placentas appear to be fused. This condition determines that for same-sex twin pairs an examination of the placenta and fetal membranes will not yield conclusive information about zygosity. About 30% of same-sex twin pairs will be MZ resulting from an embryo that split more than six days after conception. These twin pairs will be monochorionic, sharing a single placenta and chorion. The effect of chorionicity is independent of zygosity. Derom et al demonstrated that the average birth weight of dichorionic monozygotic twins was more than for monochorionic monozygotic twins (24). A described peripheral cord insertion, occurring most frequently in monochorionic twins, may play a role as an underlying mechanism responsible for an impaired uterine blood flow in monochorionic compared with dichorionic twins (25).

Monochorionic twins have an increased obstetric risk of complications such as Twin-to-Twin Transfusion Syndrome (TTS). This is a life-threatening prenatal condition for both twins in which abnormal, interconnecting blood vessels create an imbalanced blood flow that passes through one twin to the other. The “recipient” twin grows much larger because of the extra blood it receives and can develop significant cardiovascular problems as its system tries to cope. The “donor” twin receives much less blood and nutrients; so, remains smaller, and may develop severe anemia. Twin fetuses during the first and second trimester of pregnancy show a pattern of growth similar to singletons, but beyond 24 weeks gestation, the average birth weight of a fetus from a twin pregnancy shows a reduction in growth velocity with a final growth lower than that of a corresponding singleton. Furthermore, previous studies have reported that the birth weight of monochorionic twins is lower than that of dichorionic twins (26, 27).

Twins in comparison to singletons, show increased risk of prenatal death, chromosomal abnormalities, congenital malformations, perinatal mortality and morbidity. These complications are more common in monozygotic twins (28).

FGR, prematurity as well as the condition of being SGA are also more frequent in case of multiple pregnancy and are considered responsible for the well documented higher prevalence of neurodevelopmental impairment in twins compared to singletons (29, 30, 31).

6. Fetal Growth Restriction: timing and classification

Fetal nutrient supply impairment is the basic cause of secondary FGR. In front of placental impairment, the fetus in the attempt to preserve brain growth and function as well as heart and adrenal glands functions, redirects to these “noble organs” blood flow from less vital organs (for the fetus) like liver, kidneys, muscles, lungs, skin and gut. This condition, when maintained after birth, as in case of hypoxic ischemic sufferance, leads to a multiorgan failure responsible for several neonatal complications. When prolonged enough to determine a severe FGR, total body fat, lean mass, and bone mineral content are reduced, resulting in a wasted appearance of the newborn (32). Nitrogen and protein content are lower because of reduced muscle mass, and glycogen content is decreased in skeletal muscle and liver because of lower fetal plasma glucose and insulin concentrations (33).

Newborn with FGR show an increased risk of mortality and morbidity because of the compromised growth and reduced energy reserves that increase their global vulnerability during the transition from intrauterine to extrauterine life.

Two main type of FGR, symmetric and asymmetric, are usually identified. Newborns with symmetric FGR are characterized by reductions in all organ systems with the body, head, and length proportionally affected. This type of FGR begins early in gestation and usually is caused by intrinsic factors such as congenital infections or chromosomal abnormalities (34).

However, a decreased nutrient supply early in development, as in case of severe placental insufficiency, can restrict growth of all organs as well (35).

Newborns with asymmetric FGR have disproportionate growth restriction, with less affected head circumference and prevalent impairment of weight in comparison to length. As a result, the normal-sized head appears relatively large in comparison to trunk and limbs. This type of FGR begins in the late second or third trimesters, with a relative brain growth and results from reductions in fetal nutrients that limit glycogen and fat storage (35).

Some authors also enlist a 3^{rd} type termed “femur-sparing intrauterine growth restriction”. In this type, the femoral length is the only standard fetal biometric parameter unaffected while all others are reduced (36).

Clinicians have generally considered that weight parameters at birth are not sensitive measures to detect FGR (37). Thus, Ponderal Index (PI) was considered a useful tool to detect FGR, particularly in infants with asymmetric FGR, characterized by lower values. The PI is a ratio of body weight to length expressed as PI = [weight (in g) x 100] ÷ [length (in cm)], and has two great advantages; the weight and length of the newborn are relatively easy to measure and are recorded routinely in maternity hospitals, thus, enabling researchers to identify growth retardation retrospectively from historical records. PI has also been used quite apart from its use in the clinical identification of FGR; as in study on fetal macrosomia, fetal origins of cardiovascular disease, perinatal mortality and morbidity, development of type 2 diabetes in later life, developmental status and postnatal growth, maternal nutritional status and brain sparing (38, 39, 40).

Some authors have indeed expressed criticism towards the use of PI for identification of impaired fetal growth (41), but despite their misgivings, PI is still widely used as an indicator of fetal growth in studies on FGR (42, 43).

With normal growth, the PI increases gradually from 30 to 37 weeks gestation and then remains constant. A reduced PI is related to a decreased growth of adipose tissue and skeletal muscle, the major contributors to body weight. PI values allow the clinician to identify a fetal malnutrition with PI is < 10^{th} percentile (37), and severe wasting when PI < 3^{th} percentile (44).

7. Brain sparing phenomenon

The use of color Doppler ultrasonography provides noninvasive observation, confirmation and quantification of pathophysiological processes in fetoplacental circulation in pregnant women. By blood vessel mapping and the obtained waves spectral analysis, it is possible to evaluate vascular resistance of the fetus blood vessels. Umbilical arteries are the common vessels assessed by Doppler ultrasound, and several studies confirm the efficacy of middle cerebral artery (MCA) Doppler assessment and advocate it as a well-known modality for detecting fetal compromise (45, 46).

Some studies showed that MCA blood flow abnormalities were associated with hypoxia and adverse perinatal outcome as well as FGR (47), and a relationship between fetal Doppler findings and perinatal risks have been defined in numerous cross-sectional studies (48).

A ratio of MCA to UA, the cerebroplacental ratio (CPR), has been proposed as a better predictor of fetal compromise than either vessel considered alone, even when umbilical resistance index is within normal range. In the normal situation the fetal MCA has a high resistance flow which means there is minimal antegrade flow in fetal diastole while in pathological states this can turn into a low resistance flow mainly as a result of the fetal brain sparing theory (49).

The fetal brain sparing theory is one that underpins asymmetrical fetal growth restriction, where the difference between normal head circumference and decreased abdominal circumference is attributed to the fetus's ability to preferentially supply the cerebral, coronary, adrenal and splenic circulations. In a situation of chronic fetal hypoxemia, the fetus redistributes its cardiac output to maximize the oxygen supply to brain by vasodilation of the cerebral arteries thereby causing a decrease in the left ventricular afterload (50). The normal cerebroplacental ratio is >1:1, while <1:1 is considered an abnormal value. However, it is important to consider that paradoxically in some situations, such as with severe fetal cerebral edema, the flow can revert back to a high resistance pattern when the pathology has not yet resolved, then it is considered a very poor prognostic sign (51). It is now defined that brain-sparing involves specific areas rather than the global brain. Hernandez Andrade et al showed, by measuring fractional moving blood volume (FMBV), that cerebral blood flow (CBF) in FGR fetuses shows regional changes with progression of fetal deterioration. They identified an initial increase in frontal FMBV, followed by a decrease as fetal condition worsened. Basal ganglia FMBV, instead, showed a steady and significant increase with fetal deterioration. The cerebellum showed a similar trend of FMBV increase related to the severity of fetal compromise. The increase in cerebellar FMBV may also imply enhanced blood supply to the brainstem, as both are fed through the posterior cerebral circulation. This important study suggests a hierarchical order in cerebral blood supply in case of chronic hypoxia.

This peculiarity assumes considerable importance from an ontogenetic perspective; at earlier stages, higher cognitive functions of the frontal lobes are protected; however, under chronic and more threatening circumstances the focus seems to shift towards survival, protecting important structures such as the basal ganglia and the brainstem (52).

8. Fetal programming

The term “programming” refers to the process of sustaining or affecting a stimulus or impairment that occurs at a crucial point in its development (53).

The nutritional status of the mother, is an important factor that affects the programming of the body, and involves factors such as maternal body composition, maternal dietary intake, blood flow to the uterus and placenta, as well as fetus's genetic makeup. The fetus adapts to maternal malnutrition through changes in the production of fetal and placental hormones that regulate metabolism, redistribute blood flow and control growth. It is a very critical period for the ongoing development and functional maturation of organs and systems of the entire organism. This critical period coincides with the timing of rapid cell differentiation (54), thus insufficient nutrition during embryonic and fetal development results in permanent alterations to certain structural and physiological metabolic fetal functions (55).

From a strict metabolic and endocrine perspective, the immediate metabolic response of the fetus to malnutrition is to consume its substrate to produce energy through catabolism (56). Fetal undernourishment causes metabolic dependence on glucose to control the oxidation of other substrates, such as amino acids and lactic acid. Prolonged malnutrition results in delayed growth, reducing substrate use and lowering the metabolic rate, to improve fetal viability. Therefore, it can be hypothesized that the metabolic process of storing glucose continues into adulthood leading to a progressive insensitivity to insulin known as insulin resistance. In late pregnancy, when tissues and organs are rapidly developing, any growth delays significantly affect organs with consequent disproportions in organ size. The fetal attempts to protect tissues, especially brain tissue, that are critical for immediate survival through redistribution of blood flow, thus resulting in a greater loss of liver and other abdominal visceral tissue. Fetal insulin and insulin-like growth factor (IGF), which play a key role in growth control, are believed to respond rapidly to changes in fetal nutrition (56). A decline in maternal food intake and the resulting drop in maternal IGF may trigger decreases in fetal insulin, IGF and glucose levels. This drop reduces the transfer of amino acids and glucose from the mother to the fetus and ultimately slows the rate of fetal growth (57, 58).

When the fetus has limited nutrient availability, anabolic growth control hormones, such as IGF-1 and insulin, decrease while the concentration levels of catabolic hormones like glucocorticoids, a major contributor to cell differentiation, increase (59).

British epidemiologist Barker first noted the inverse relationship between weight at birth and risk of cardiovascular disease formulating the fetal environment as a new component in the etiology of cardiovascular disease (60).

The "Barker hypothesis,” which states such programmed changes during this critical period predispose the fetus to certain postnatal diseases and suggests that such developmental metabolic and endocrine derailment can be felt throughout life (61).

Nowadays FGR is considered an antecedent to some adult-onset disorders, including hyperlipidemia hypertension, coronary heart disease and diabetes mellitus.

9. Neonatal clinical profile of FGR infants

The FGR infants are prone to present with several complications after birth. These complications include; perinatal asphyxia with low Apgar score, then necessitating of neonatal resuscitation; frequent meconium aspiration, with increased risk of air leak syndrome; persistent pulmonary hypertension necessitating of prolonged intensive ventilatory assistance; hypothermia with increased risk of neonatal sepsis due to immunological system temporary impairment; hypoglycemia, a very dangerous complication, leading to potential brain impairment with seizures and following high rate of developmental impairment and polycythemia correlated with an increased risk of cerebral venous thrombosis and stroke.

An increased risk of necrotizing enterocolitis is also reported requiring total parenteral nutrition with prolonged hospital stay (62).

The FGR infant at hospital discharge should be enrolled in an individualized developmental and auxological follow-up. Several operative strategies can be applied by the pediatrician or child neuropsychiatrist (63).

Domains of developmental surveillance and early intervention include potential developmental and cognitive impairments; such as cerebral palsy necessitating of individualized physiotherapy as well as pharmacological and surgical option availability, gross motor and minor neurologic dysfunction, poor visuo-motor perception with reading and mathematics learning difficulties leading to poor academic performance requiring special education, behavioral problems (oppositive defiant disorder and attention deficit hyperactivity disorder) for which the best approach is based on systemic relational and cognitive behavioral therapy (64, 65, 66).

10. Long-term consequences

After the first identification of increased risk of metabolic and cardiovascular diseases in the adult age, overlapping with the so called "Metabolic syndrome X", several other long-term consequences linked to FGR and the concomitant fetal programming condition have been widely described.

A recent review considered the aforementioned FGR related pathology in adult life (67), these included several diseases ranging from organ specific functional impairments to condition affecting neurological and cognitive domains (Table 2)

The increased risk of obesity has been also related to altered central leptin signal (68).

Long-term consequences of FGR
Cardiovascular disorder, hypertension
Diabetes mellitus
Overweight, obesity
Immune dysfunction
Osteoporosis
Lung abnormalities; reactive airways disease
Liver disease
Kidney disease
Polycystic ovarian syndrome, premature pubarche
Cancer (breast, ovarian, colon, lung, blood)
Parkinsonism
Alzheimer disease
Schizophrenia, depression, anxiety, bipolar disorder
Social problems
Shortened life span

Table 2. Principal long-term consequences of fetal growth restriction.

11. Conclusions

FGR is a condition that involves a substantial number of both at-term and pre-term newborns, at risk of several negative developmental consequences. Therefore, prerogative of neonatologist should be an individualized care during hospital stay and, at hospital discharge, the infant transition to the pediatrician for the enrollment in an individualized auxological and developmental follow-up program.

Adult medicine should similarly increase the level of a broad-spectrum surveillance in individuals born with FGR, with the aim to increase a healthy lifestyle, based on constant physical activity, healthy eating habits and early individualized intervention.

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