

## Intrauterine Growth Retardation, Fetal Growth Restriction: Impact on Brain Development

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### Abstract

**Objective:** Review the current state of knowledge on intrauterine growth retardation (IUGR) and growth restriction and assess the medium- and long-term future of children.

**Method:** Bibliographical research carried out by consulting the Pub Med database and the recommendations of learned societies using the following English terms: "Small for gestational age", "foetal growth restriction", "intra uterine growth restriction", "Neuro-developmental outcomes".

**Results:** Intrauterine growth retardation is a dynamic abnormality of fetal growth that can lead to hypotrophy. Its definition is based on the observation of weight, and on the purely statistical concept of average weight observed by gestational age in the population.

Growth restriction indicates that the fetus has not been able to reach its growth potential. This potential is determined by taking into account factors that physiologically influence intrauterine growth, including parity, age, height, weight, weight index, ethnic origin of the mother and sex of the child.

Intrauterine growth retardation is one of the main risk factors for perinatal mortality.

Newborns with IUGR have increased neurological morbidity in the form of spastic diplegia, mental retardation, a broad spectrum of learning deficits and cognitive development disorders, combined with an association with neuro-psychiatric diseases and metabolic syndrome in adulthood.

**Conclusion:** The developing organism adapts to the environment in which it is located. These adjustments induce IUGR, but also long-term consequences.

Because of increased risk of long-term neuro-developmental and psychiatric disorders, the newborns with IUGR requires early detection and appropriate management by obstetricians. The pediatrician must be attentive to normal psychomotor development of these children, establish specific neuro developmental care and watch for the appearance of the metabolic syndrome.

**Keywords:** *Intra Uterine Growth Retardation; Growth Restriction; Metabolic Syndrome; Neurological Outcome*

### Introduction

Intrauterine growth retardation (IUGR) is one of the major risk factors for perinatal mortality and morbidity. This is one of the major concerns of obstetricians and neonatologists. IUGR is defined as the inability of the fetus to achieve genetically determined potential growth due to a variety of causes. It indicates alteration in the nutrition of the fetus with fetal, maternal, placental or extrinsic origin [1].

IUGR is therefore a dynamic concept that implies that the fetus cannot reach its growth potential in relation to what is expected and which results in a slowdown or even a halt in growth.

The concept of intrauterine growth retardation assumes that fetal growth has been delayed by a pathological process.

For many years, attention has been drawn to the need to consider genetic, maternal and / or obstetrical factors to identify an abnormality of fetal development and, gradually, the term fetal growth restriction has appeared in the literature.

It is also necessary to distinguish between children with a low birth weight, a child who is constitutionally small but has reached its growth potential, and another child who has a real restriction of growth related to a pathological process involving significant risks of complications in the short and long term.

The term fetal growth restriction is used in reference to an intrauterine growth abnormality defined not in relation to a mean birth weight but to a theoretical weight given the genetic (or constitutional) growth potential of the fetus. This growth potential can be approached by customizing growth curves.

Growth restriction is therefore defined by insufficient growth of the fetus relative to its genetically programmed growth potential. Each fetus inherits growth potential, determined by factors that physiologically influence intrauterine growth such as parity, age, weight, height, ethnicity of the mother, and sex of the child.

Thus, a newborn who is considered hypotrophic according to a standard growth curve is not necessarily affected by stunting. It can be constitutionally small [2].

### Physiopathology of fetal growth

Fetal growth requires the supply of nutrients regulated by placental and fetal factors. The fetal growth process goes through three phases:

- The first is the phase of rapid increase in the number of cells, or hyperplasia, until the 16<sup>th</sup> week.
- The second is the phase of increase in number and size of cells, between the 16<sup>th</sup> and the 32<sup>nd</sup> week.
- The third is the phase of increase in cell size, or hypertrophy, from the 32<sup>nd</sup> week of gestation; it is during this phase that the fat and glycogen stores are formed [3,4].

When the first phase is impaired, the growth is reached early and will affect all organs. In this case, the RCIU is symmetrical. It is estimated that 25% of the IUGR are associated with early involvement [5,6].

During an alteration of the second or third phase, the organ involvement is asymmetrical (75% of the IUGR). This asymmetrical delay may be secondary to placental insufficiency.

This asymmetry of growth is due to the fact that the fetus adapts and redistributes cardiac output to vital organs, and brain and heart growth can be particularly spared. Fetal growth is dependent on fetal insulin-like growth factor 2 (IGF-2), the secretion of which depends on placental lactogenic hormone (hLP). After the 20<sup>th</sup> week, fast growth is dependent on fetal insulin and insulin like growth factor 1 (IGF-1), but it also depends on other, lesser known factors [3,4,6]. These factors play a role in protein synthesis and in fetal carbohydrate metabolism. The fetal secretion of IGF-1 does not depend on fetal pituitary growth hormone (GH) but is primarily regulated by the nutritional status of the fetus. It is at birth that the control of the secretion of IGF-1 becomes dependent on GH. It is likely that hLP and placental GH play a role in fetal growth, but the precise mechanism of action is unknown.

The placenta supports fetal growth from the 4<sup>th</sup> month. The growth is maximum in the 2<sup>nd</sup> quarter on the statural plane and in the 3<sup>rd</sup> quarter on the weight plan.

Fetal growth is proportional to placental growth but not linear, and lack of placental growth in late pregnancy is a factor limiting fetal growth. Fetal growth slows near the end. The presence of male fetal androgens may explain the differences in mean weight observed between boys and girls.

### Regulation of fetal growth

Different factors influence fetal growth: genetic, fetal, maternal or circulatory factors [7].

### The role of the placenta

The placenta is the privileged site of fetal-maternal exchanges.

It has endocrine, immunological and filtration functions. It is involved in breathing, nutrition, protection of the fetus against infectious and toxic aggression, and in the hormonal balance of pregnancy.

Fetal growth requires the supply of nutrients. It seems that during the first part of pregnancy, the fetal growth is conditioned by the tissue specificity of certain enzymes linked to genetic factors, and in the second half, it is the placental and nutritional factors that play a preponderant role. It is from the fourth month that fetal growth is actually supported by the placenta. The fetal metabolism is then conditioned by the placental contribution of the nutrients. Maternal glucose is the main energy element; carbohydrate metabolism uses 80% of the fetal oxygen at term. The concentration of amino acids is multiplied by three compared to that of the adult. In contrast, free fatty acids are in low concentration.

### Placental pathologies

#### Vascular disease and uteroplacental insufficiency

Uteroplacental circulation is essential for optimal nutrient and oxygen supply. The maternal flow reaches the intervillous chamber through the spiral arteries. Histological and morphological changes in these arteries are explained by the trophoblastic invasion which takes place in two phases.

Uteroplacental insufficiency is thought to be due to an abnormal placentation, more precisely an anomaly of the trophoblastic invasion. This lack of invasion leads to a certain number of vascular phenomena, namely:

- An absence of vasodilation of the placental supply vessels;
- Vascular obliteration by trophoblastic material (emboli);
- A capacity retained by the vessels to respond by vasoconstriction to vasopressin hormones.

This results in insufficient flow resulting in placental ischemia.

However, these vascular anomalies of placentation are far from being the sole cause of placental insufficiency; the other mechanism is the endothelial "disease" that would result in a cascade of events. The endothelial cell releases excess of endothelin and thromboxane, which are potent vasoconstrictors; these two factors increase sensitivity to angiotensin, promote elevation of vascular resistance and consequently arterial hypertension. In addition, the injured endothelial cell releases fewer vasodilator factors, mainly prostaglandin (PGI<sub>2</sub>) and nitric oxide. Impairment of the balance between these different factors causes not only vascular vasoconstriction and vascular endothelial lesions, but also activation of the coagulation cascade, an increase in platelet aggregation that is associated with a risk of microthrombi, especially at the placental level.

These events lead to vasoconstriction, microangiopathy and disseminated microcoagulopathy (DIC). These lesions can reach the central nervous system, the kidney (genesis of pre-eclampsia) and the liver; with the clinical consequence of the genesis of HELLP syndrome (Hemolysis, Elevated Liver enzyme, Low platelets). The placentation anomaly and the endothelial lesions are at the origin of many clinical forms of the gravid pathology whose intrauterine growth retardation is only one aspect. Finally, the different mechanisms are far from clear and many lines of research are under way.

### Uteroplacental insufficiency

Normal fetal growth is partly related to the mother's contribution to the fetus of nutritional substrates and oxygen, and the excretion by the fetus of carbon dioxide and metabolites produced by her body. These exchanges are conditioned by the placenta, as well as uter-

ine and umbilical circulation. Any factor suddenly interrupting the uteroplacental circulation causes fetal hypoxia. Chronic reduction of uteroplacental exchange results in not only a reduction in oxygen supply, but also a reduction in the availability of glucose and glycogen stores, as well as a reduction in the fetal-maternal ratio of essential amino acids. The consequences are a decrease or even a cessation of fetal growth, a reduction in fetal activity and a vascular redistribution to the noble organs (the heart, the brain and the adrenal glands) [8].

Finally, fetal hypoxia and hypoglycaemia could lead to a decrease in the secretion of insulin, which is a growth hormone, or an increase in the factors that inhibit the action of insulin and IGF-2.

### Etiologies of growth abnormalities

Normal fetal growth depends on maternal, fetal and placental factors and external factors that are associated with an intrinsically presumably genetically pre-established potential.

### Fetal etiologies of IUGR

#### Fetal chromosomal aberrations:

In particular, the following are at issue:

- Trisomies 13, 18 and 21, as well as monosomy X or Turner's syndrome.
- Chromosomal abnormalities of structure: deletions (Prader-Willi syndrome, Cat's cry syndrome, Wolf- Hirschhorn syndrome, etc.)
- Mosaics confined to the placenta: trisomy 16.
- Uniparental disomies.

The practice of amniocentesis with fetal karyotype study should be part of the early IUGR or IUGR assessment associated with other ultrasound signs.

### Congenital malformation syndromes

Smith-Lemli Opitz Syndrome, Cornelia de Lange Syndrome, Silver Russell Syndrome, etc.

### Constitutional bone diseases or skeletal dysplasias

The most frequently encountered are dyschondrosteosis, hypochondroplasia, pseudo-hyperparathyroidism and polyepiphyseal dysplasias.

Signs of ultrasound calls and/or family history associated with antenatal suspicion of IUGR may guide the etiologic assessment.

### Infections

Mainly involved: cytomegalovirus, rubella, herpes, parvovirus, Epstein-Barr Virus, HIV, toxoplasmosis and syphilis.

The search for arguments in favor of one of these infections is part of the systematic antenatal assessment in case of IUGR.

### Maternal etiologies of IUGR

Vascular causes, including pre-eclampsia, account for about 40% of IUGR.

#### Vascular causes

These diseases are characterized by a decrease in uteroplacental flow.

A history of vascular insufficiency such as chronic hypertension (hypertension), diabetes, lupus and acquired or hereditary thrombotic diseases are risk factors for the development of pre-eclampsia.

### Toxic causes

Tobacco use leads to growth restriction by a vasoconstrictor mechanism of the uterine artery. It is a dose-dependent risk factor, which alone accounts for 9% (for premature infants) to 12% (for full term infants) of hypotrophy [9].

There is also an influence of the consumption of alcohol, drugs and certain treatments such as antiepileptics, betablockers, immunosuppressants or corticosteroids on birth weight [10,11].

### Deficiency of nutritional intake

Poor nutritional status antepartum or weight gain below 7 kg during pregnancy is a risk factor for IUGR [12].

### Uterine malformation, hypoplasia and fibroma

These pathologies cause changes in the uterine environment and may interfere with fetal development.

### Maternal pathologies leading to chronic hypoxia

These are chronic diseases, such as severe maternal anemia, respiratory failure, cyanogenic heart disease, homozygous sickle cell disease, etc.

### Predisposing terrains

Primiparity, history of IUGR or pre-eclampsia, close pregnancies, prolonged exposure to altitude, poor socio-economic background, prolonged stress, arduous work or maternal age greater than 35 years or less at age 20 are risk factors for IUGR [13].

### Uteroplacental etiologies of IUGR

Pathologies or malformations affecting the uteroplacental unit and the cord can be the cause of poor fetal vascularization and therefore of IUGR. We can cite for example the phenomena causing placental ischemia or hypovascularization (pre-eclampsia, eclampsia, HELLP syndrome...), chorangiomas and hemangiomas, placental implantation abnormalities such as placenta previa, as well as any funicular anomaly: single umbilical artery, small cord, velamentous insertion.

### Other factors influencing fetal weight

These parameters are factors described as varying birth weight, but this is not considered pathological.

### Sex

Birth weight varies according to the sex of the child with, for the same gestational age, a higher weight in boys.

This variation in weight by sex is physiological and is not correlated with an increase in the incidence of pathologies related to low birth weight.

### Multiple pregnancies

The growth of fetuses from a twin pregnancy is identical to that of fetuses from a single pregnancy until the age of 31 to 34 weeks of amenorrhea. Any shift in growth before this term should motivate an etiological investigation.

### The delay in intra uterine growth

Conventionally, the definition of normal weight was based on the observation of the weights of birth, and on the purely statistical concept of mean observed by gestational age in population. Under the assumption of a normal weight-for-gestational age distribution, the average is frequently replaced by the 50<sup>th</sup> percentile. Standard deviation is used to define the threshold weights corresponding to the percentiles. The usual definition of PAG uses the 10<sup>th</sup> percentile and selects 10% of the smallest children by GA. The births futures are a sufficiently homogeneous and large group so that the pace of the weight distribution is symmetrical. Outside the term, the size of the

samples, the heterogeneity of the weights linked to the pathologies associated with prematurity, and the absence of certain methodological precautions lead to an asymmetrical appearance of the distribution of the weight. The percentiles observed are sometimes nonetheless used, resulting in the Anglo Saxons call it “crude curves” or rough curves [14]. At the 10<sup>th</sup> percentile, this solution allows you to select exactly the 10% of children with the lowest weights.

IUGR is a dynamic abnormality of fetal growth that can lead to hypotrophy. It is diagnosed with repeated fetal echocardiograms (at least two exams three weeks apart) that demonstrate pathological fetal growth such as growth reversal or stunting [15].

### Restriction of growth

The term fetal growth restriction is used in reference to an intrauterine growth abnormality defined not in relation to a mean birth weight but to a theoretical weight given the genetic (or constitutional) growth potential of the fetus.

Intra uterine growth restriction indicates that the fetus was unable to reach its growth potential. This potential is determined by taking into account factors that physiologically influence intrauterine growth, including: parity, age, height, weight, weight index, mother's ethnicity, and sex. 'child [16]. This is a dynamic definition and the diagnosis is most often made after repeated evaluation of fetal growth.

The restriction refers to a dynamic notion and is used to describe an insufficient state of advancement compared to an expected evolution. It is therefore appropriate to designate an inflected trajectory of fetal growth leading to a weight defect.

Thus, a newborn who is considered hypotrophic on anthropometric references is not necessarily affected by an intrauterine growth restriction if it is constitutionally small and a newborn affected by an intrauterine growth restriction is not necessarily hypotrophic.

### Evolution

Intrauterine growth retardation is one of the major risk factors for perinatal and neonatal mortality and morbidity

### Death rate

In term newborns, several studies have shown that the risk of neonatal mortality is higher in PAG neonates than in eutrophic neonates [17,18].

A recently published meta-analysis that included developing countries showed that the risk of death in term newborns with PAG was higher with OR = 2.4 [95% CI: 1.7 - 3.6] [19].

### Immediate neonatal consequences of IUGR

#### Respiratory complications

In the term newborn, the study by Mc Entire, *et al.* has shown an increased risk of respiratory distress in very severe stunting (inferior 3<sup>rd</sup> percentile) [20]. The risk of intubation in the birth room was significantly higher in this group (2.2% versus 0.6%, reference group 26<sup>th</sup> - 75<sup>th</sup> percentile,  $p < 0.001$ ). There was no difference in the case of a more moderate PAG.

#### Neurological consequences

PAG term neonates have a significantly higher risk of maladaptation to ectopic life compared with eutrophic neonates. Thus, in a retrospective study of Ananth, *et al.* showed that the Apgar score < 7 at 5 minutes of life was significantly higher in PAG neonates: RR adjusted = 2.0 [95% CI: 1.9 - 2.1] [18].

#### Digestive consequences

Low birth weight for gestational age is a risk factor for digestive disorders that may progress to ulcerative necrotizing enterocolitis, especially in premature infants. These disorders are thought to be favored by chronic fetal hypoxia, which causes vascular redistribution

favoring cerebral circulation at the expense of mesenteric vascularization [21]. Other possible mechanisms are a decrease in the length of the intestinal tract, an alteration of the villi and the size of the liver [22].

### Metabolic consequences

The main metabolic problems observed in the neonatal period are hypoglycemia and hypocalcemia. The risk of hypoglycemia is major especially in the first 72 hours of life. It is linked to low levels of glycogen and lipids (little adipose tissue), which deprives tissues of alternative substrates and increases tissue demand for glucose [23]. In addition to limited fat stores in adipose tissue, oxidation of fatty acids is dysfunctional. Deficiency of ketone bodies particularly exposes children to the neurological sequelae of hypoglycaemia [24]. There is hyperinsulinism or increased sensitivity to insulin that may exacerbate hypoglycaemia [22]. The risk of hypoglycemia is increased by the joint occurrence of perinatal asphyxia, hypothermia and/or polycythemia that increases tissue glucose consumption.

### Hematological consequences

Chronic fetal hypoxia, related to placental dysfunction, is responsible for an increased synthesis of erythropoietin responsible for increasing the overall mass of the red line with polycythemia and thrombocytopenia [25]. The incidence of polycythemia (hematocrit > 65%) was significantly increased in PAG neonates (17%) compared with eutrophic neonates of the same term (5%) [26].

### Infectious consequences

The infectious risk, secondary to leuconutropenia, is associated with low birth weight. This risk is greater in premature infants. This susceptibility to infections is explained by a deficiency of humoral immunity (decreased concentration of immunoglobulin G) and cellular immunity (decrease of the phagocytic index) and by neutropenia. However, the use of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in children premature with PAG has not been shown to be effective in the prevention of secondary sepsis [27].

### Becoming long-term

#### Neurological consequences

Classically, IUGR is associated with a higher risk of minor cognitive deficits, symptoms of hyperactivity, inattention, and academic difficulties. Premature newborns with IUGR present increased neurological morbidity in the form of spastic diplegia, mental retardation, a wide spectrum of learning deficits and cognitive impairment, and an association with neuropsychiatric adulthood. Maternal stress, placental insufficiency, pulmonary maturation and treatment of chronic lung disease expose the fetus and prematurity to an excess of corticosteroids with consequent neuro-developmental delays. In the first week of life, neuroimaging techniques revealed a significant reduction in total brain volume and cortical gray matter in neonates with IUGR on placental vascular insufficiency. These decreases persisted at the age of the term [28]. Early neuro-developmental evaluation showed a reduction in attention-interaction skills with a correlation between cortical gray matter volume and these attentional abilities. Lodygensky, *et al.* [29] have thus shown that the hippocampus, a structure implicated in memory and learning functions and which is very susceptible to hypoxia, nutrient deficiency and stress hormones, shows a decrease in volume. premature with RCIU compared to premature normal birth weight.

In a large Australian cohort, the authors found that severe growth restriction (birth weight < 3<sup>th</sup> percentile), defined as an optimal birth weight percentage equal to the weight observed on the optimal customized weight, was associated with increased risk. low to moderate intellectual retardation in term and preterm infants, adjusted for socio-demographic factors; the impact was greater in term infants [30]. As for severe intellectual deficit, the risk was four times higher in cases of severe growth restriction (< 3<sup>th</sup> percentile) in term infants.

In conclusion, intrauterine growth retardation appears to have a negative impact on cognitive, neurodevelopmental and behavioral outcomes in full-term infants. This risk is greater in the case of the most severe stunting < 3<sup>th</sup> percentile.

### Metabolic consequences

In the longer term, IUGR is associated with a risk of developing metabolic diseases, metabolic syndrome or “syndrome X” (high blood pressure, type 2 diabetes, and other organs such as the liver) in adulthood. This phenomenon is called “fetal programming”. This

hypothesis was formulated by Barker, *et al.* and is known as “Barker’s hypothesis” [31]. The fetus with IUGR would be programmed to develop a “thrifty” phenotype with an increase in food intake, fat storage and possibly a decrease in energy consumption. This hypothesis was evoked following epidemiological studies carried out in individuals born during the winter of 1944 - 1945 in the famine-starving Netherlands, which showed that maternal food deprivation was associated with a decrease in birth weight, fetal malnutrition essentially amino acids, and a decrease in the function and number of beta cells in the pancreas. Therefore, in adulthood there is an increase in insulin resistance, obesity, and arterial hypertension [31,32]. Barker’s epidemiological studies have shown that markers of malnutrition at birth, such as low birth weight, low weight for gestational age and IUGR, increase the risk of hypertension, hyperlipidemia, obesity and from diabetes to adulthood. Barker, *et al.* have also shown an increased risk of death from coronary heart disease or stroke in adulthood [33]. Fetal programming could be accomplished by irreversible epigenetic modifications (methylation, DNA acetylation, histone modification) of chromatin modulating gene expression.

### Conclusion

The developing organism adapts to the environment in which it is located. These adjustments induce intrauterine growth retardation (IUGR), but also long-term consequences. The increased risk of long-term neurodevelopmental and psychiatric disorders in infants with intrauterine growth retardation require early detection of RCIU and its management by obstetricians. The pediatrician should be attentive to the good psychomotor development of these children, establish neurological management developmental development and watch for the onset of the metabolic syndrome.

### Conflict of Interest

No conflicts of interest.

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