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Professional paper

PREVENTION OF FETAL GROWTH RETARDATION

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Abstract

Fetal growth restriction (FGR) has been a frequently encountered pathology in obstetrics and affects 5-10% of pregnancies. It has been one of the three main causes of perinatal deaths, after premature births and fetal malformations. In approximately one third of cases with FGR, cause or pathology was not found, which made it difficult to prevent or treat them effectively. Mostly, FGR was a consequence of insufficiency of uteroplacental circulation, placental and fetoplacental function. The term SGA (small for gestational age) has to do with constitutional growth rates and the statistical determination within which the newborn is considered smaller for gestational age. Whereas the term FGR (fetal growth retardation) refers to delayed growth below the 10th percentile as a pathological phenomenon. The current management of FGR consists of fetal surveillance to detect a decline in the baby's health and deliver when this can be safely done. Therefor Doppler ultrasound was considered the chosen technique. The use of low-dose aspirin for preventing FGR and preeclampsia (PE) has been one of the most important research topics for the last 10 years. Several national protocols recommend the treatment with low-dose aspirin (100-150mg daily) for high-risk pregnancies, starting around 12-16 weeks of gestation. It favors placentation by its proangiogenic, antithrombotic and anti-inflammatory effects.

Keywords: low-dose aspirin, fetal growth retardation, preeclampsia

Introduction

The prevalence of fetal growth retardation varies depending on factors such as maternal health, socioeconomic status and geographical location. Fetuses with normal weight were found in the 50th percentile, while fetuses with FGR were in the 10th percentile. The current management of FGR consisted of fetal surveillance to detect a decline in the baby's health and deliver when this can be safely done. The best methods to diagnose FGR typically involves a combination of ultrasound measurements, particularly fetal biometry, along with dopplers blood flow studies to assess blood flow in the umbilical artery, uterine artery and middle cerebral artery. Although in the last four decades we have a clear relief in terms of monitoring pathological pregnancies through ultrasound, still FGR is one of the three main causes of perinatal deaths, after premature births and fetal malformations. In approximately one third of cases with FGR, their cause or pathology is not found, which makes it difficult to prevent or treat them effectively. In order to assess FGR, there are curves according to which the average weight for each gestational age is determined, as well as standard deviations. According to this, fetal growth retardation is considered when we have a level below two standard deviations. (Figure 1)

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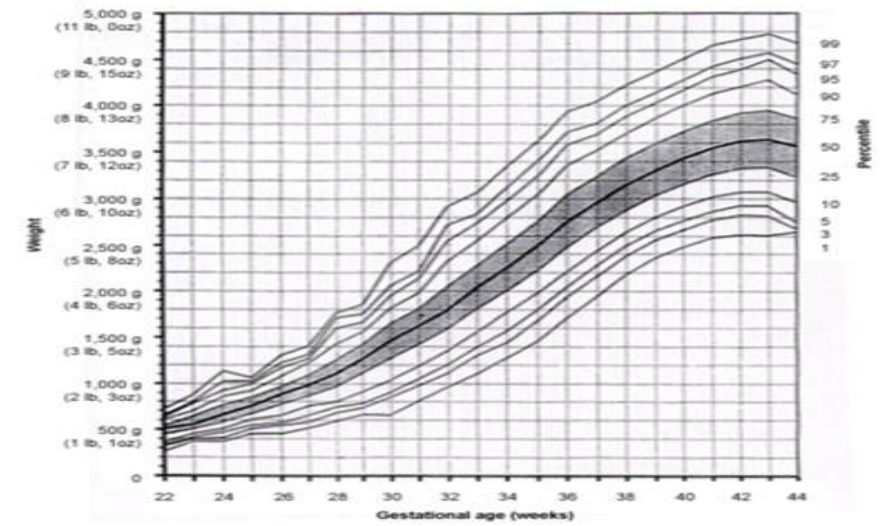

Figure 1. (Jaypee Digital)

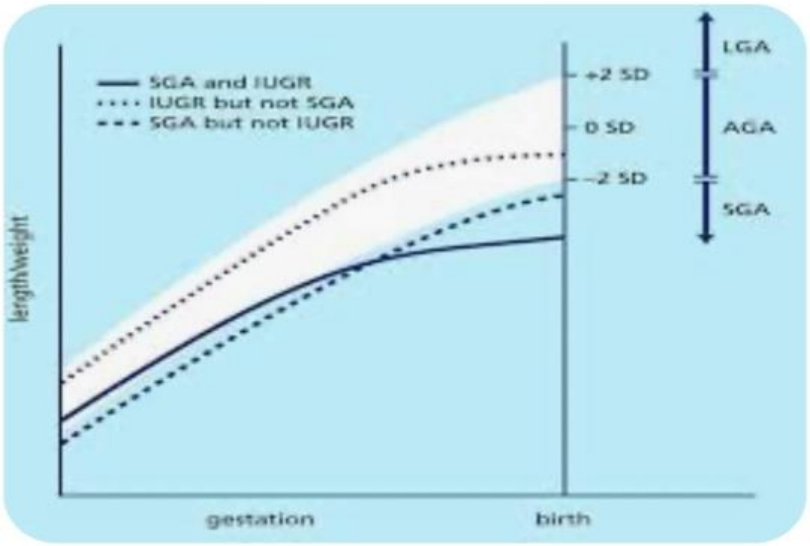

Figure 2. (MAGIC Foundation)

Eutrophic are considered small newborns from the genetic and constitutional point of view, in which we do not have delayed growth. (Figure 2)

The term SGA (small for gestational age) has to do with constitutional growth rates and the statistical determination within which the newborn is considered smaller for gestational age.

Whereas the term IUGR (intrauterine growth retardation) refers to delayed growth below the 10th percentile as a pathological phenomenon, which is based on ultrasound and other diagnostic methods. (Table 1).

Table 1. (Intech Open)

	IUGR	SGA
Perinatal outcomes	Worse	Similar to normal fetuses
Growth delay	"True"	"Constitutional"
Doppler ultrasound	Hemodynamic redistribution	Normal
Abnormal environment adaptation	Present	Absent
Preeclampsia risk	Higher	Lower

Types of IUGR

There are two types:

-Type 1, where the growth delay is earlier and affects both weight and height; it is also called symmetrical or total delay and

- Type 2, where the reduction of weight and not of height is more pronounced, i.e. only the transversal abdominal diameter is smaller, while the BPD and femur grow normally; otherwise, it is also called asymmetric delay.

In type 1, the reduced weight is not as pronounced as in type 2. Genetic and chromosomal disorders and TORCH infections are counted as the most frequent causes of type 1. Total IUGR is more serious, the earlier it appears.

Whereas the most frequent causes of type 2 are placental insufficiency, pregnancy-induced hypertension and maternal malnutrition.

Formula for weight calculation: PI= weight in gr•100/ (length in cm)3

Fetal growth dynamics

For the dynamics of fetal growth, several parameters are taken into account: biparietal and abdominal circumference, head and thorax, femur length, weight and length of the fetus. According to some data, the first 12 weeks the normal weight gain is 5 g/day, up to 21 weeks it is 10 g/day and up to 37 weeks 20 g/day. At first there is cell proliferation and later increase in cell size. In the first 20 weeks the growth is moderate, from 20-38 weeks the growth accelerates, and then slows down.

Factors that influence fetal growth

There are many factors affecting growth regulation, but the main ones are placental and fetal. In cases with IUGR, the addition of amino acids to the mother's diet would have little effect, because for good fetal growth it is necessary for the nutrients to reach the intervillous chambers, normal placental function is needed, as well as placental and fetal growth factors.

1. *The influence of the uteroplacental circulation on the growth of the fetus*

If the flow of nutrients decreases in the intervillous chambers, as a result, we will have insufficiency of uteroplacental circulation. This then affects the decrease in the concentration of glucose, which if it falls below 60 mg/100 ml, does not pass to the placenta. That is, even if the mother receives sufficient amounts of glucose through food, but has reduced uteroplacental circulation, the fetus may not grow normally. So, IUGR is a consequence of insufficiency of uteroplacental circulation, placental and fetoplacental function.

2. Placenta influence on fetal growth

The final growth of the placenta is achieved in the fifth month of pregnancy. The volume, weight, surface area and anatomy of the placenta have a direct influence on fetal growth. A placenta with a large villous surface normally allowing good fetal growth. Placentas weighing under 350gr. have a tendency to be insufficient. Also, the hormonal and metabolic function of the placenta play an important role, such as the placental lactogenic hormone-HLP which uses fatty acids that save maternal glucose for the mother's needs and simultaneously increase its amount for use by the fetus.
Placenta and umbilical cord pathologies:

- narrow caliber chorion vases
- more villas with sub-standard length
- avascular villus
- inflammation of decidual and spiral arteries
- placental abruption
- partial hydatids moles
- subchordal fibrin deposits
- in pronounced hypotrophies, more microinfarcts
- leukocytic infiltrates
- tight umbilical cord knots
- hemangioma of the placenta
- velamentous and peripheral cord insertions
- the single umbilical artery
- multiple burden
- enzyme defects, etc.

3. The influence of fetal factors on the growth of the fetus

The high amount of prolactin in the amniotic fluid, especially in the first 3 months (when there is a level of 2500 ng/ml; at term 1000 ng/ml), speaks of its importance in regulating the water and electrolyte exchanges.
The concentration of growth hormone in the pituitary gland increases 66 times from the start. The exact mechanism of action is not known, but it is known that its deficit is associated with fetal restriction, while the injection of growth hormone in preterm baby’s has no effects on growth.
The nervous system and hypothalamus cause insulin-like effects on fibroblast growth, the nervous system, and the development of the brain itself. For example, hypothalamus deficiency in anencephaly causes major growth disorders.
Fetal causes

- twin pregnancies with vascular anastomoses
- chromosomal anomalies
- different genetic syndromes
- metabolic disorders
- major congenital anomalies

4. Nutritive substances

Maternal glucose is the main source of energy for the fetus. A small part of the fetal glucose is oxidized for energy needs, the rest is deposited as glycogen in the liver and muscles.
Amino acids in the fetal blood have a concentration 3 times higher than in the maternal blood, they are necessary for the construction of proteins.
Free fatty acids in the fetus have a concentration equal to 1/6 of the maternal plasma concentration and are not of any special importance in the fetal metabolism.
Minerals, vitamins, and insulin are necessary for protein synthesis and cell growth. The increase in fetal insulin synthesis enables the use of glucose for fetal metabolism and growth. Absence or decreased secretion of insulin causes IUGR. Actually, insulin is the first fetal growth hormone.
The decreased secretion of fetal thyroid hormones affects the decrease in oxygen consumption and decrease in the perfusion of tissues.
Somatomedin is found in the fetal circulation, in the kidneys, liver and muscles of the fetus. Its activity is controlled by insulin and HLP; in restricted cases, its level is lower.
There is evidence that zinc has an impact on prostaglandin synthesis and that its deficiency affects FGR.
All these factors, together with normal oxygenation, condition the functioning of fetal metabolism. Daily diet with 2550 kilocalories is considered sufficient.
There are multiple causes that are responsible for intrauterine growth retardation.

5. Maternal or preplacental reasons

•mother's age (below 16 and over 35)
•parity (none or over 5 births)
•ethnic affiliation and race
•interval between two pregnancies (shorter than 6 months or longer than 120 months or more)
heavy physical work and prolonged standing (this causes an increase in the venous pressure of the inferior vena cava, a decrease in blood volume, and thus placental flow)
•BMI below 20, weight during pregnancy below 45kg or above 75kg
•assisted reproduction
•previous SGA birth
•some maternal pathologies (such as hematological and immunological disorders, decompensated cardiopathies, bronchial asthma and pneumonia with respiratory failure, severe anemia)
•maternal disorders (arterial hypertension [pre-existing or pregnancy-induced], diabetes with vasculopathy, renal diseases, systemic lupus erythematosus, antiphospholipid syndrome)
chronic maternal intoxications (smoking, alcohol, narcotics)
•maternal therapy (warfarin, steroids, anticonvulsants, antiepileptics, antineoplastics, antagonists of folic acid)
•infectious diseases (recurrent urinary tract infections, bacterial, viral or parasitic infections [TORCH, syphilis, tuberculosis, HIV or malaria])
•abnormalities of uterine vascularization (hypoplastic uterus, especially in primiparous women, fibroids, placenta insertion pathologies, such as insertion in the uterine septum or in the lower segment where the vascularization is weaker)
•vascular renal syndromes

These pathologies are the main etiological factor and require careful monitoring. This includes chronic hypertension, pregnancy induced hypertension and pre-eclampsia. They can appear as specific or as overlapping on a renal or vascular pathology. Systolic arterial pressure over 140 mm Hg and diastolic over 90 mm Hg in pregnant women at rest, speaks of the possibility of restriction, while over 160 mm Hg, it can endanger fetal viability. Hypertensive disease during pregnancy causes placental vascular damage and reduction of blood flow. An increased arterial pressure above normal values during pregnancy is usually accompanied by proteinuria. Proteinuria is defined as an increase in the amount of protein in urine above 300mg/24 hours. A protein value of 1+ or more in urine is considered abnormal. It should be taken into account that urinary infections can also be the cause of proteinuria.
In pregnancies suffering from pre-eclampsia, there is an increase in toxic factors released by damaged endothelial cells of uteroplacental vessels. Pre-eclampsia usually presents in the second half of pregnancy with hypertension and proteinuria, and can result in intrauterine growth retardation, fetal distress, premature birth, low birth weight, and intrauterine death.
Cases with diabetes complicated by pronounced degenerative vascular damage may also cause fetal growth retardation.
In order to prevent the effects of pre-eclampsia on the fetus in time, it is necessary to carry out the screening of pre-eclampsia which coincides with the time of the first screening of the fetus, around the 12-13 week of pregnancy. For this screening you need:

-anamnesis
-doppler of the uterine arteries (pathological)
-measuring the blood pressure, (above 140/90 mm Hg in pregnant women is considered pathological)
-measuring the level of specific biomarkers such as PAPP-A and PIGF (which decrease and cause vasoconstriction of the endothelium of spiral arteries)

If the screening results are positive, it is necessary to start early with small-dose aspirin therapy, preferably before the 16th week, in order to prevent negative effects.

6. *Idiopathic fetal hypotrophy (1/3 of the cases remain without etiological diagnosis)*

Diagnosis

To make the diagnosis, it must be proven that there is no wrong estimation of the gestational age, the etiology must be tried and the degree of damage must be assessed.
The history and measurement of the uterine height are taken into account as a guiding element. While ultrasound is considered the chosen technique. Other necessary examinations re Doppler flowmetry, fetal biophysical profile determination and CTG monitoring.

1. With the ultrasound, the age of the pregnancy can be estimated (more precisely, until the 12th week); biometry assessment and construction of fetal growth curves; evaluation and prognosis of intrauterine growth of the fetus.

Gestational age is based on the date of the last cycle.

-Measurement of the gestational sac between weeks 5-7 (GS - with a difference of 5 days)
-Cranio-caudal distance is measured between weeks 7-13 (CRL - with a difference of 3 days)
-Cephalometry (BPD)
-Abdominal diameter (transverse and anteroposterior- AC),
-Femur (from the 13th week)
-Measurement of the amount of amniotic fluid (AFI-measurement of the amniotic index)

Before 34 weeks of amenorrhea, measurement of biparietal and femur circumferences better predict fetal weight. The diagnosis of fetal retardation is more certain if the transversal abdominal diameter is below normal.

2. Doppler ultrasound uses variations in the frequency of ultrasound reflected by moving erythrocytes and thus allows determining placental flows. In this way, the ratios of systole and diastole are determined and specific indicators are used, such as resistance indicator, pulsation indicator, maximum systolic velocity, maximum diastolic velocity and their average.

The flowmetry curves belong to the umbilical artery, a. uterine, a. cerebri media and aorta.
In cases with fetal retardation, resistance in umbilical artery is increased and decreased in ACM.

2.1. Reduction of diastolic flow in umbilical artery is an alarm sign. If in a fetus with IUGR the Doppler flow of AU drops to zero or becomes negative (ARED flow), then this is associated with a bad perinatal outcome, as there is a risk of cardiovascular and metabolic deterioration of the fetus. In case of AU with an increased pulsation >95 percentile, weekly ultrasound follow-up is necessary and the ACM and DV Doppler should be added to the examination. (Figure 3).

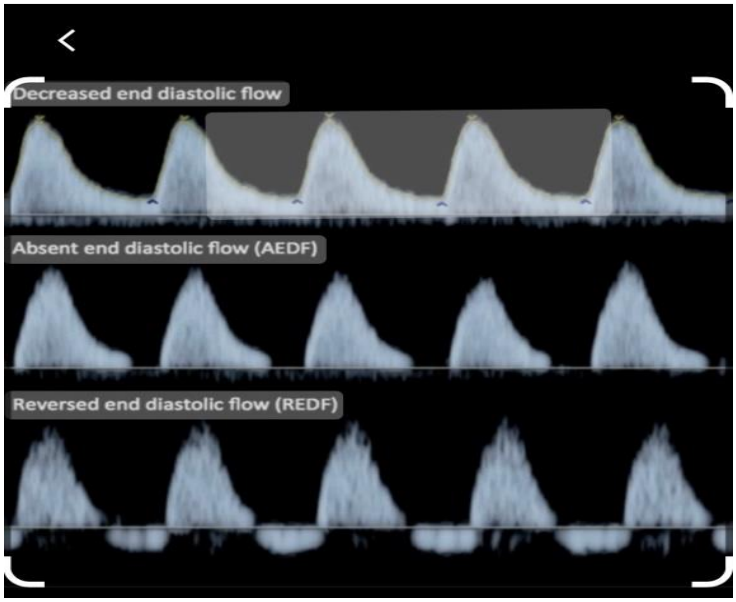

Figure 3. (Springer Link)

2.2. The Doppler of the ACM provides data on the fetal hemodynamic state. Normally in cerebral arteries we have high resistance with increased pulsation. In cases where hypoxia increases, compensatory vasodilatation of these arteries appears with the aim of increasing oxygenation (brain-sparing effect). This vasodilatation in Doppler is expressed by a decrease in the pulsation of the ACM below the 5th percentile as a sign of hypoxia and is considered pathological. Doppler of the ACM is considered valuable monitoring especially in late IUGR, especially when the Doppler of the AU is normal.

2.3. The next Doppler used as a predictor of fetal distress is the CPR (cerebroplacental ratio), a coefficient that gives the ratio between the pulsation index of the ACM and AU; the lower it is - the more expressed the pathology.

2.4. An important Doppler that presents an obvious sign of threat or presence of acidity and fatal risk for the fetus with advanced IUGR is that of DV (ductus venosus). This proves that we have compromised circulation in the venous system. Myocardial hypoxia leads to a limitation of the cardiac function and an increase in the pressure in the right atrium, namely the central venous pressure. As a consequence, we have a decrease in diastole, namely an increase in pulsation in the DV, as well as in other veins. The pulsation in DV increases so much, until it comes to the loss of the positive -a wave. Even here, the appearance of ARED flow of the -a wave speaks of very pronounced acidemia, which doubles the lethal risk every day, and survival for more than a week is almost impossible, regardless of the week of pregnancy.

3. The fetal biophysical profile is served by 5 parameters:

-respiratory movements
-fetal movements
-fetal tone
-amount of amniotic fluid
-heart rate

The first four parameters are ultrasound and the fifth is cardiotocographic. Each indicator is assessed with 0-2 points; the maximum score is 10. An indicator equal to or below 6 indicates fetal distress and should be repeated every 48 hours.

4. CTG recording is a simple method of monitoring that provides important data on the state of the fetus. The parameters that this method uses (Fisher Score) are: basal frequency, accelerations, variability, width, oscillation and decelerations. For each parameter, the assessment is done with 0-2 points, and when we get indicators from 9-12 points, we talk about fetal well-being, while from 0-6 points we are dealing with a severe fetal condition.

5. The oxytocin test (CST) is a method that requires 20 minutes of recording, then oxytocin perfusion is established which is gradually increased until 3 contractions appear in 10 minutes. The test is contraindicated in cases with a risk of premature birth and placenta previa. The prognosis is severe with a positive test in fetuses with FGR and with oligohydramnios at the 31-35th week of amenorrhea.

If FGR is detected after the 27th week of pregnancy, hospitalization is recommended to assess the condition: umbilical flowmetry, ultrasound for possible abnormalities, CTG 3 times/day, blood pressure measurement every 4 hours, laboratory analyzes such as uricemia, blood glucose with glucose load, serology for TORCH and hemostasis. If these examinations are in order, the patient is discharged to stay at home with a recommendation for CTG every 3 days and echo and doppler check every 2 weeks. If a pathology such as pre-eclampsia, diabetes or pathological doppler is found in the art. umbilical cord, then hospitalization continues with occasional early examinations and eventually the administration of adequate therapy such as antihypertensive therapy, antiplatelet therapy, calcium supplementation, corticosteroid therapy, adequate nutritional diet for the mother, etc.

The classification of fetuses with IUGR is based on fetal biometry, measurement of abdominal circumference, Doppler flowmetry, amniotic fluid quantity and clinical parameters.

Classification of IUGR

- Stage 0, fetuses with weight or AC under the 10th percentile; Doppler of normal AU and ACM
- Stage I, fetus with weight and AC below the 10th percentile, plus abnormal Doppler of AU and ACM

• Stage II, fetuses with weight and AC below the 10th percentile, plus Doppler absent or reverse AU type
• Stage III, fetuses with weight and AC below the 10th percentile, plus Doppler absent or reverse type of Ductus Venosus (DV).

The only effective treatment is the termination of the pregnancy. If it is necessary to end the pregnancy before the 34th week, it is decided for this when the risk of prematurity is considered lower than staying in the uterus, since the fetus is anyway brought out in an unfavorable environment. Here, several parameters are taken into account: the weight must be at least 1000 gr; stopping the growth of the BP diameter as well as the non-reactive CTG track are considered alarm signs.

Management of IUGR cases according to gestational age:

-before the 30th week and weight under 1000gr, the attitude is expectant,

-between the 30-32nd week and weight up to 1500gr., the termination of the pregnancy is planned if there is a threat of further intrauterine restriction,

-from the 32nd week and weight over 1500gr., the pregnancy is terminated before severe damage to the fetus occurs,

-after the 36th week, pregnancy can continue if regular growth continues.

Mode of birth:

-between the 28th and 36th week, it is performed by cesarean section

-after the 37th week it depends on the circumstances and can be spontaneous or operative.

Prevention of fetal growth retardation

Our purpose was to estimate the effect of low-dose aspirin started in early pregnancy on the incidence of fetal growth restriction and preeclampsia in women identified as being at risk of preeclampsia. 150 pregnant women at risk of PE had to receive low-dose aspirin (100-150 mg) daily. The first group (out of 75 women) began therapy at 12 weeks, while the second group (out of 75 women) began after week 16. Both groups were followed up to term with respective ultrasound and doppler examinations. The reduction of FGR was significant in the group of women who started low- dose aspirin at 12 weeks. The increase in mean birth weight was 196g (CI 107-285g) when aspirin was started before 16 weeks of gestation or less compared with 70g (CI 15-124g) when aspirin was started after 16 weeks.

Evolution of IUGR children

The development progress of children born with IUGR depends on the time of occurrence of IUGR and its degree.

Favorable cases when IUGR appears after the 32nd week and we have compensation/ redistribution of perfusion in order to protect the most sensitive organs against metabolic disorders and anoxia, such as the brain and heart.

Cases that can have consequences when IUGR appears early, (but not before 26-28 weeks) and we still have a head circumference growth advantage.

If BIP and AC continue to fail to develop here, i.e. signs of anoxia appear, fetal distress worsens and decompensation of redistribution begins. In the CTG we have a flat (silent) recording and in the Doppler diastole is absent.

Cases of IUGR with a severe prognosis are harmonic hypotrophies that start quickly before the third trimester, such as deficiency in the development of cerebral structures and acute fetal distress.

Newborns with IUGR have several characteristic features of malnutrition:

• larger head compared to other parts of the body

- superior anterior fontanel
- lack of buccal adipose tissue (cheeks)
- lack of abdominal adipose tissue
- low muscle mass and subcutaneous tissue
- thinner umbilical cord
- thin, dry skin
- longer nails
- extremities relatively longer compared to the body
- wrinkles/skin folds in the neck, armpits, inter-scapular space and gluteal region
- newborns in an agitated state.

To calculate the malnutrition of the newborn there is the so-called Ponderal Index:
PI= weight in gr • 100/ length in cm
PI below the 10th percentile speaks for malnourishment of the neonate, below the 3rd percentile major malnutrition.
Early complications in neonates with IUGR:
hypothermia, hypoglycemia, hemoconcentration, hypocalcemia, hydrolytic disorders, respiratory problems.
Late complications:
delayed neurological growth and development when they reach school age and adulthood, are predisposed to chronic diseases typical of adulthood since childhood or adolescence.

Conclusion

Fetal growth retardation is a complex syndrome with many factors, not all of them sufficiently clarified and with limited treatment possibilities. The goal in the treatment of FGR remains to prevent and evaluate the degree of severity and to determine the most appropriate time of termination of labor.
Daily low-dose aspirin initiated before 16 weeks of gestation was associated with a significant decrease in the incidence of preeclampsia, fetal growth retardation and preterm birth in women identified to be at risk for preeclampsia.
The gestational age is the key factor for treatment. Before the 30th week, the prognosis is usually grave with high mortality and neurological sequelae. After the 31st week, perinatal deaths are few and fetal extraction is worthwhile, before signs of decompensation appear. The decision about this should be made after consultation between obstetricians and neonatologists

Nomenclature

AC Abdominal circumference
ACM Middle brain artery
AFI Amnio-fluid index
ARED Flow Absent reverse end-diastolic flow
AU Umbilical artery
BMI Body mass index
BP Biparietal diameter
CPR Cerebroplacental ratio
CRL Craniocaudal length
CST Contraction stress test
CTG Cardiotocography
DV Ductus venosus
FGR Fetal growth retardation

GS gestational sac
HIV Human immunodeficiency virus
HPL Placental lactogenic hormone
IUGR Intrauterine growth retardation
PE Preeclampsia
PI Pulsation index
TORCH Toxoplasmosis- rubeola- cytomegalovirus- herpes simplex
PAPP Pregnancy-associated plasma protein A
PI Ponderal index
PIGF placental growth factor
SGA Small for gestational age

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