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# Managing intrauterine growth restriction

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## ABSTRACT

The fetal growth normally depends on sufficient delivery of oxygen and nutrients mainly via the placenta. Inadequate fetal nutrition may result in poor development and adaptation that permanently alter the fetus' metabolism and physiology. Intrauterine Growth Restriction is defined as a deviation on the fetal growth pattern. An estimated fetal weight (EFW) that is below the 10th percentile for gestational age is commonly used to describe fetal growth restriction. Usually obtained sonographically, there is evidence that ultrasound imaging of the uterine artery, middle cerebral artery, and fetal umbilical artery during the late third-trimester (approximately 35-37 weeks) significantly improves the detection and diagnosis of IUGR. In obstetrics, an increased risk of perinatal mortality and morbidity is associated with the diagnosis of IUGR.

**Keywords:** Intrauterine growth restriction (IUGR), growth retardation, fetal growth, small for gestational age (SGA), symmetrical IUGR, asymmetrical IUGR, placental insufficiency, umbilical artery Doppler, pulsatility index

## INTRODUCTION

**IUGR** or **Intrauterine Growth Restriction** is defined as an obstetric condition where the fetal growth is below normal (fetal weight is estimated below the 10th percentile for its gestational age) commonly associated with high risk of stillbirth and perinatal morbidity and mortality. The American Congress of Obstetricians and Gynecologists (ACOG) recommends this definition, however, various global definitions include estimation of fetal weight cut-off values below the fifth and third percentiles [1,2].

It affects 5-10% of pregnancies, being the second most common cause of perinatal death and over 30% of stillbirths. Intrauterine growth restriction increases the likelihood of perinatal morbidity and mortality as well as long-term health problems in adults that include cardiovascular or endocrine diseases as well as impaired neurological and cognitive development. Due to constitutional factors like ethnicity, approximately 70% of fetuses are classified as weighing below the 10th percentile. We must differentiate fetal growth restriction of small-for-gestational age. Small-for-gestational-age includes healthy but constitutionally small fetuses with a lower risk of abnormal perinatal outcomes in addition to those with true fetal growth restriction [3].

## METHODS

As part of this descriptive review, studies published in the last 10 years were gathered from PubMed and NCBI database. Studies were searched using keywords such as intrauterine growth restriction (IUGR), growth retardation, fetal growth, small for gestational age (SGA), symmetrical IUGR, asymmetrical IUGR, placental insufficiency, umbilical ar-

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tery Doppler and pulsatility index to analyze the most common causes as well as evaluate this condition. This article aims to highlight the crucial role of ultrasound in the prompt diagnosis of IUGR and management of this condition.

## RESULTS

### Intrauterine growth restriction vs small for gestational age

Genetics, nutrition, and intrauterine conditions all have an impact on growth. The risk of neonatal pathology can be determined using growth parameters and gestational age. The growth parameters that are measured at birth aid in predicting future growth, development, and the risk of diseases [4].

The terms IUGR and small for gestational age (SGA) have been used synonymously in medical literature, but with small differences between them.

The term small-for-gestational-age has been used for those infants whose birth weight is below the 10th percentile for that particular gestational age or two standard deviations below the population norms on the growth charts, which are not affected by IUGR, normally with a good perinatal prognosis. SGA only provides a measure of size, using the Fenton growth charts and not a direct measure of antenatal growth quality, providing a more precise assessment of growth vs gestational age. The parameters are length, weight, and head circumference, with separate charts for boys and girls, as it can be seen in the chart below, Figure 1 [1].

The growth of the fetus, as well as the function of the placenta, depends on the maternal factors (such as the maternal health status, nutritional status, smoking or drug use). Fetal growth restriction (FGR) is commonly associated with placental insufficiency, in which the fetus cannot reach its intrinsic growth potential because of impaired placental function. There are many types of placental lesions that may cause placental-related FGR, including poor remodeling of the uterine spiral arteries during early pregnancy, leading to maternal vascular malperfusion, as it can be observed in Figure 2 [5,6]. Size of the placenta directly affects nutrient transfer through surface area changes [7].

### Doppler assessment

The umbilical artery carries nutrient-depleted blood from fetal circulation to the placenta. The pulsatility index is a parameter used in Doppler assessment and can be calculated by dividing the peak

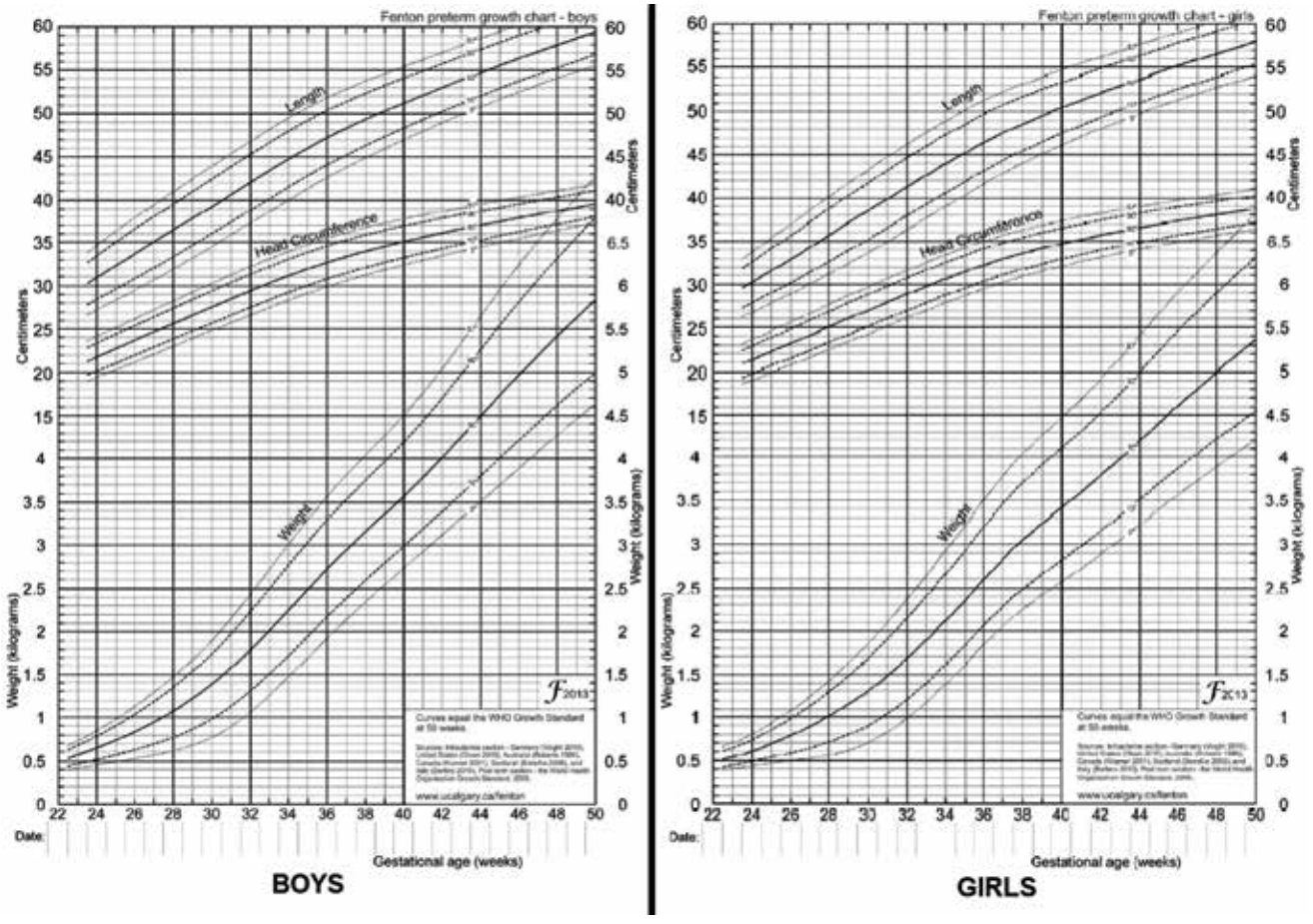



**FIGURE 1.** Fenton growth charts – https://www.msdmanuals.com/professional/pediatrics/perinatal-problems/growth-parameters-in-neonates

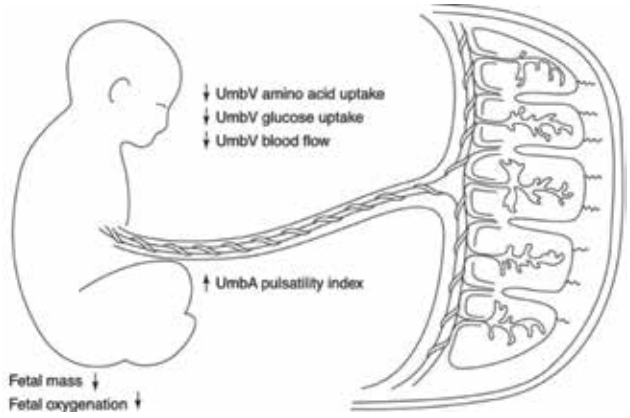



**FIGURE 2.** Placental involvement in fetal growth restriction

systolic velocity minus the end-diastolic velocity by the time-averaged velocity (PI = (PSV - EDV) / TAV) [6].

The normal pulsatility index in Doppler finding is usually under 95%. It can be elevated (>95%), or it can have an absent or reversed end-diastolic blood flow. The pulsatility index increases when there is decreased end-diastolic flow due to reduced placental perfusion and utero-placental insufficiency as seen in IUGR. Pregnancies with IUGR that associate an abnormal pulsatility index on the umbilical artery can be associated with increased risk of adverse perinatal outcomes [1].

A fetus with severe growth restriction first has decreased end-diastolic flow in the umbilical artery and then has increased end-diastolic flow in the middle cerebral artery, as shown in Figure 3. Following this, there are changes in the venosus circulation, such as pulsatile flow in the umbilical vein and decreased forward flow in the ductus venosus during atrial systole. For IUGR the most reliable diagnostic tool next to UA-PI is the MCA-PI, also used as a noninvasive procedure in detecting fetal anemia [8,9].

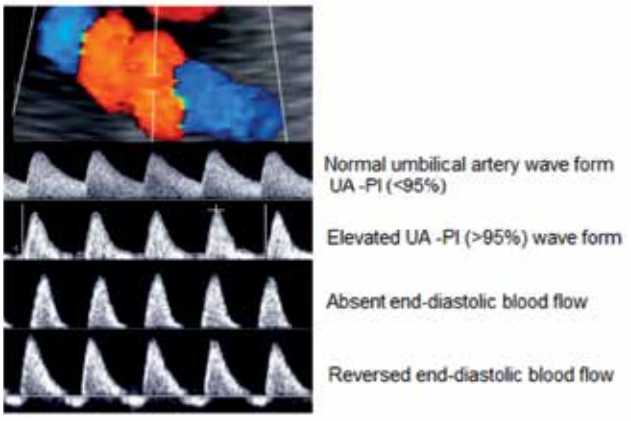



**FIGURE 3.** Umbilical artery Doppler evaluation.

However, according to studies, the strongest Doppler parameter for predicting the short-term risk of fetal death in early-onset FGR is the Ductus Venosus Doppler when flow waveforms only become abnormal in the advanced stages of fetal compromise. A growth-restricted fetus's hemodynamic status can be assessed using Doppler ultrasound of the ductus venosus and middle cerebral artery, but its clinical value has not yet been established [2,4,10].

Some studies suggest that a decrease in PI of the anterior cerebral artery maximizes cerebral perfusion in fetuses with impaired growth, suggesting that the may be a better predictor of the brain sparing effect [8].

Growth restriction occurs naturally in two types, one with an early onset and one with a late onset, which has its own biochemical, histological, and clinical characteristics. Due to its association with maternal hypertensive disorders, pattern of deterioration, and severity of placental dysfunction, early onset FGR differs from late-onset FGR. The obstetrician faces a serious dilemma when making the diagnosis of early onset FGR because of the clinically obvious fetal and maternal manifestations. The fetus must be delivered in order to address the issue of the deprived environment. Necrotizing enterocolitis, respiratory distress syndrome, and neonatal death are all prematurity-related complications that can occur during delivery [7].

The early onset form is often diagnosed with abnormal umbilical artery Doppler and often is associated with preeclampsia, whereas the late onset form has a weaker association with preeclampsia, is more prevalent, and exhibits less change in umbilical flow patterns [4,5]. In early-onset IUGR, end-diastolic velocities are absent or reversed, and they are observed about one week before acute deterioration. In addition to 40 percent of fetuses with acidosis showing this umbilical flow pattern, a recent series of severely compromised IUGR fetuses suggests that such a finding can be used to predict perinatal mortality and morbidity independently of gestational age [4].

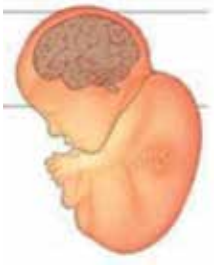
Unlike abnormal umbilical artery Dopplers that are associated with adverse perinatal and neurodevelopmental outcomes, small fetuses with normal umbilical artery Doppler represent one end of the normal-size spectrum, and the need to treat them differently from true IUGR babies who had been stressed.

## Types of IUGR

The placenta is a crucial organ for the development and health of the fetus. A decrease in maternal blood flow to the growing fetus results from either maternal or fetal vascular compromise in the placenta, process that can lead to IUGR [11].

Normally there are two different types of IUGR as shown in Table 1:

**TABLE 1.** Types of IUGR [6,8,12]

| |  |  |
|---|---|---|
| | **PRIMARY IUGR or SYMMETRIC IUGR** | **SECONDARY IUGR or ASYMMETRIC IUGR** |
| **Characteristics** | Characterized by the entire body being proportionally small and all internal organs being reduced in size. It accounts for 20% to 25% of all cases of IUGR. | Characterized by the head and brain being normal in size, but the abdomen is smaller, evident until the third trimester, due to decreased liver size, scrawny limbs because of decreased muscle mass and thinned skin because of decreased fat. |
| **Period** | Earlier gestation | Later gestation |
| **Incidence** | 20-30% | 70-80% |
| **Etiology** | Genetic disorders or infection | Utero-placental insufficiency |
| **BPD, HC, AC and FL** | All proportionally reduced | AC decreased<br>BPD, HC and FL are normal |
| **Cell number and size** | Reduced and Normal | Normal and Reduced |
| **Ponderal Index** | Normal (more than 2) | Low (less than 2) |
| **Anthropometry (weight, length and HC)** | Reduction in all parameters | Reduction in weight and length<br>Head circumference is normal (brain sparing growth effect) |
| **Difference between head and chest circumference** | Less than 3 cm | More than 3 cm |
| **Malnutrition features** | Less pronounced | More pronounced |
| **Prognosis** | Poor | Good |

Some studies manage to classify FGR into types I, II, and III by utilizing the head circumference to abdominal circumference (HC/AC) ratio to distinguish between symmetrical or proportionally small fetuses and asymmetrical fetuses, or those with a disproportionately slower growth of AC [3].

There is a frequent epidemiologic distinction between early-onset and late-onset FGR. Early onset FGR is far less common (0.5-1%) than late onset FGR (5%-10%), but it has a much greater clinical impact because of the high mortality and morbidity incidence [5].

In order to assess intrauterine growth-restricted fetuses, fetal biometry is measured including expected fetal weight [EFW], abdominal circumference [AC], and Doppler cardiovascular changes. Additionally, amniotic fluid volume is measured as well as clinical parameters. For each IUGR fetus the amniotic fluid index will be either AFI <5 cm or AFI ≥5 cm. It applies to all pregnancies regardless of gestational age. The classification includes as shown in Table 2 [6].

The inability of a fetus to grow to its full potential is known as late-onset fetal growth restriction and is diagnosed after 32 weeks of pregnancy. Late-onset fetal growth restriction is associated with an increased risk of short- and long-term adverse outcomes, including hypoxemia and mild neurodevelopmental delay, in comparison to fetuses that are normally grown, despite the fact that the burden of perinatal complications is lower in late-onset disease than in early-onset disease. Some findings show that approximately one third of pregnancies complicated by late-onset growth restriction result in adverse perinatal outcomes [13].

A major perinatal risk factor for neurodevelopment is preterm birth. According to a meta-analysis, children with IUGR had worse cognitive function for the first 12 years of their lives. Those with IUGR and SGA had significantly lower cognitive scores than those with AGA (appropriate for gestational age) [14].

**TABLE 2.** Stages of IUGR [6]

| | **EFW or an AC** | **Doppler (UA and MCA)** |
|---|---|---|
| **Stage 0** | <10th percentile | normal |
| **Stage I** | <10th percentile | abnormal |
| **Stage II** | <10th percentile | absent or reversed Doppler flow of the UA |
| **Stage III** | <10th percentile | absent or reversed Doppler flow of the DV |

### Etiology and early detection

Four biometric measures are typically used to detect fetal growth: 1) biparietal diameter, 2) head circumference, 3) abdominal circumference, and 4) femur length. Those biometric measures are added together to calculate an estimated fetal weight. When umbilical artery Doppler velocimetry is added to conventional antepartum testing in the presence of fetal growth restriction, the incidence of perinatal mortality is lowered by up to 30% [15]. To diagnose IUGR the following methods can be used: fundal height (does not coincide with gestational age), measurements calculated in ultrasound (that does not coincide with gestational age and are smaller) and Doppler ultrasound with abnormal findings.

While it may seem that the identification of the optimal delivery time is the only way to manage IUGR during the third trimester, scientific evidence suggests that placenta-mediated complications, including IUGR, and the most severe complications, can be detected as early as the first trimester of pregnancy. It is recommended that women who have two or more current pregnancy risk factors, such as pre-gestational hypertension, obesity, maternal age greater than 40 years, artificial reproductive technology use history, pre-gestational diabetes mellitus (type I or II), multiple gestations, and a history of placental abruption or infarction, receive low-dose aspirin. Aspirin initiated in early pregnancy may prevent many of these complications. It should begin around 12 to 16 weeks of pregnancy and last up to 36 weeks [16,17].

During pregnancy, nutrients are provided to the fetus through maternal circulation and placental transport. There is evidence that IUGR is primarily caused by fetal etiologies, such as genetic abnormalities (syndromes, chromosome abnormalities), maternal factors (vascular disease, persistent hypoxia and undernutrition, and toxins), and placental etiologies. According to estimates, 40% of birth weight is attributed to genetic factors while 60% is attributed to environmental factors. The pathogenesis of IUGR is influenced by poor macronutrient provision and inadequate micronutrient supply to the fetus. It has been shown that inadequate nutrition can alter fetal physiological processes through epigenetic mechanisms, resulting not only in altered growth phenotypes in the short term, but also in dysregulation of metabolic and cardiovascular processes in adulthood when resources are not aligned with programmed responses [18].

Intrauterine Growth Restriction may cause premature birth or low birth weight, decreased oxygen intake, hypoglycemia, low Apgar, low resistance to infection, risk of meconium aspiration (which can lead to respiratory distress syndrome), poor temperature regulation, polycythemia and hyper viscosity and in most severe cases, stillbirth. Greater risk of developing IUGR can be seen in the following conditions as shown in Table 3 [6,9,15].

**TABLE 3.** Causes of IUGR

| |
|---|
| • Umbilical cord abnormalities |
| • Placental abnormalities |
| • Birth defects or chromosomal abnormalities |
| • Pregnancy-induced Hypertension |
| • Gestational Diabetes |
| • Oligohydramnios |
| • Multiple pregnancies |
| • Teratogen exposure |
| • Maternal weight under 100 pounds |
| • Poor nutrition during pregnancy |
| • Use of cigarettes, alcohol, drugs |

In order to correctly identify the cause of FGR, a detailed family and maternal history is necessary, which should include details such as: maternal age, ethnicity, height and weight, nutritional status, socioeconomic status, medications, smoking or drug use, chronic medical conditions, personal or family history that suggests thrombophilia, genetic disorders or consanguinity, obstetric history (birthweight of previous children) and ultrasound confirmation of pregnancy dating [9].

Fetal growth restriction is connected with specific chromosomal abnormalities. IUGR affects at least 50% of fetuses with trisomy 13 or trisomy 18. It is also more likely to occur in fetuses who do not have chromosomal or genetic abnormalities but have a variety of structural malformations (congenital heart disease or gastroschisis) [15].

The most prevalent pathology that is linked to fetal growth restriction is abnormal placentation or the presence of a single umbilical artery that results in poor placental perfusion, or placental insufficiency. Maternal vascular malperfusion is the most commonly observed placental disease associated with FGR [19].

Multiple pregnancies are associated with an increased risk of mortality and morbidity compared with singleton pregnancies. Fetal growth restriction, preterm birth, and perinatal loss are more prevalent in twin pregnancies. With nearly twice the rate of growth restriction and a higher incidence, monochorionic twin pregnancies are more likely to be complicated by FGR than dichorionic twin pregnancies. Fetal growth monitoring is essential, since growth restriction and weight discordance are a major cause of mortality and morbidity [4,20].

During pregnancy, metabolic changes caused by diabetes can have an impact on the development and function of the uteroplacental and fetoplacental units. As a result of type 1 diabetes, fetal growth may be affected in two directions, such as maternal

hyperglycemia stimulating overgrowth, and maternal vasculopathy leading to placental insufficiency altering nutrient transport and causing IUGR [21].

The most severe forms of preeclampsia that are also associated with deep placentation disorders and uteroplacental insufficiency can now be diagnosed using a combination of biophysical, ultrasonographic and biochemical markers during the first trimester. As a result, such screening can be used indirectly to detect cases of preterm IUGR that are associated with preeclampsia. However, such screening is not specifically focused on detecting IUGR at an early stage, which could therefore provide opportunities for improvement.

Fetal growth restriction has been linked to exposure to certain substances and medications. Tabacco, alcohol, cocaine, and narcotics are among the substances that have been linked to SGA and IUGR. Any medication's effect is determined by the drug's inherent teratogenicity, duration of exposure, dosage, and individual genetic predisposition to drug metabolism. SGA was linked to extremely low protein intake prior to 26 weeks of gestation and severe caloric restriction was linked to moderate weight loss at birth [15].

## Clinical features

Fetal sizes below the 10th percentile account for about 40% of babies who are healthy and small. In contrast to FGR, which is a pathologic condition in which the fetus is starved of nutrition and oxygen (hypoxia), the fetus in FGR is constitutionally small but not necessarily small. Multiple factors influence the intricate processes of fetal growth and development. Pregnancy-induced hypertension, preeclampsia, malnutrition, chronic anemia, and other negative environmental stimuli cause the fetus to have unbalanced nutritional requirements and supplies, which in turn causes IUGR. The hypothalamic-pituitary-adrenal axis, metabolic, endocrine, and cardiovascular systems are all affected by these changes [22]. Fetal clinical features as shown in table 4, such us (Table 4).

Clinically, the first step is the distinction between 'true' fetal growth restriction, with abnormal feto-placental function and poorer perinatal outcomes, and constitutional small-for-gestational age, with a near-normal outcome. It is not sufficient to rely solely on umbilical artery Doppler to make a diagnosis nowadays, since this index detects only early-onset severe cases. A perinatal outcome related to FGR is predicted by the presence of factors associated with a poorer fetal outcome, such as a high Doppler cerebroplacental ratio, essentially a diagnostic index, a low uterine artery Doppler, and a growth centile below the third [10].

## Management of intrauterine growth retardation

Women with suspected FGR should undergo systematic assessment that includes a detailed history. General management measures include treatment of maternal disease, proper nutrition during pregnancy and bed rest. To prevent fetal hypoxia, the fetus should be continuously monitored throughout labor. Serial ultrasonography can be used to properly evaluate the majority of fetuses with limited growth every 3-4 weeks. The frequency of ultrasound growth assessments should not exceed every two weeks [15].

**TABEL 4.** Clinical features in infants with IUGR [6,23]

| |
|---|
| Low weight (600 g below the minimum in percentile standard |
| Large Head circumference compared to than the body (brain sparing effect) |
| Relatively large hands and feet compared to body |
| Thin appearance due to reduced muscle mass and subcutaneous fat, easy peelable skin |
| Meconium strained vernix and umbilical cord. The umbilical cord might appear to be short and thin |
| Dry and wrinkled skin, "wizened facies", refers to sunken facial features with absent buccal fat that look like those of an elderly person – "old man" |
| Inadequate formation of breast buds, long finger nails and immature female genitalia |

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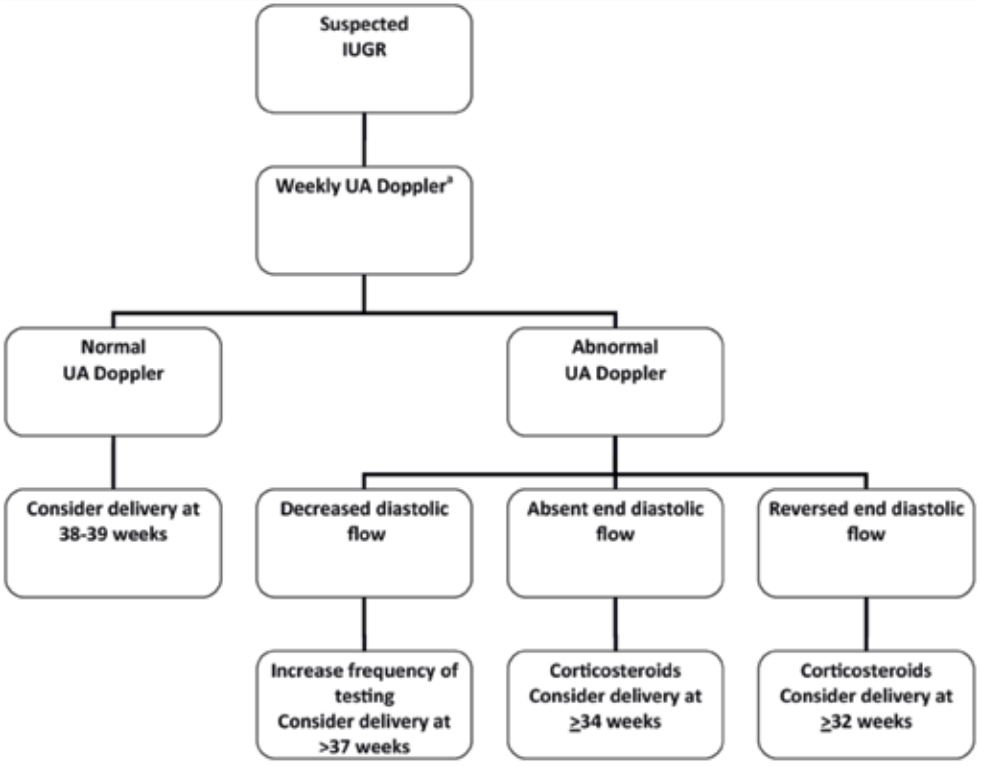


**FIGURE 4.** Doppler ultrasound in the management of IUGR

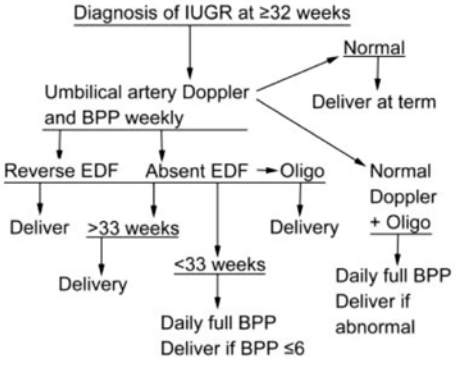


**FIGURE 5.** Diagnosis of IUGR in the third trimester

If the fetus exhibits abnormal function on biophysical profile testing, preterm delivery is indicated.

The management of IUGR must be individualized for each patient, and it can be observed in Figure 4 and Figure 5.

The primary strategies for managing these fetuses are the evaluation of fetal vitality and determining when delivery should occur because there is no effective treatment to reverse or stop the progression of placental insufficiency. The use of aspirin, bed rest, oxygen, and maternal nutritional supplements have all been studied in an effort to develop a treatment for FGR [3,22].

When nonstress tests, biophysical profiles, or both, are used in conjunction with standard fetal surveillance, umbilical artery Doppler velocimetry is associated with improved outcomes in fetuses with fetal growth restriction. If delivery is anticipated before 32-33 weeks of gestation, antenatal corticosteroids are recommended due to their association with improved preterm neonatal outcomes [15].

Further examination of the fetal circulatory system by Doppler examination of the middle cerebral artery, ductus venosus, and umbilical vein can be considered in the event that abnormal umbilical artery Doppler studies are present [9,17].

Due to the fact that delivery is the only current treatment for IUGR, the most important factor is the right timing, balancing the risk of iatrogenic morbidity and continued exposure to an unfavorable intrauterine environment.

## CONCLUSION

The placenta is a crucial organ to the growth and development of the fetus. Placental insufficiency, or the inability of the placenta to supply the fetus with enough oxygen and nutrients, causes intrauterine growth restriction. IUGR affects up to 5-10% of pregnancies. Since SGA is not the same as IUGR, the diagnostic uncertainty for fetuses with growth restriction is greatly increased. These IUGR fetuses will be managed using both monitoring and delivery methods. The following are management principles in a pregnancy with a suspected growth-restricted fetus

such us appropriate maternal and fetal care, close monitoring of the fetus, maternal activity limitation, providing oxygen to the mother if needed for fetal oxygenation improvement, assessment of fetal well-being and coordinate delivery.

In some studies, abnormal umbilical artery Doppler velocimetry defined as a pulsatility index greater than the 95th percentile or absence or reversed end-diastolic flow was associated with adverse perinatal outcomes in growth-restricted fetuses in the strongest and most significant manner. Doppler velocimetry must be integrated with biophysical profiling in order to determine the optimal timing of delivery. A comprehensive sonogram should be taken to look for fetal anomalies and karyotyping should be considered to rule out aneuploidy in addition to managing any maternal illness. A fetal chromosomal disorder or an infection could cause symmetric restriction and the patient may decide to have an amniocentesis or other diagnostic procedure because of this possibility. While many infants with growth restrictions are constitutionally small, it should be kept in mind that some of them do not have any evidence of growth restriction. The severity and progression of IUGR can only be determined through serial ultrasound examinations.

An infant suffering from IUGR or SGA is clearly at greater risk for mortality than an infant of appropriate gestational age due to various factors, including the etiology of the condition, its duration, and its severity of the effects.

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