REVIEW ARTICLE

Maternal-Fetal Work-up and Management in Intrauterine Growth Restriction (IUGR)

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ABSTRACT

Intrauterine growth restriction remains befundling problem in obstetrics, dependent on multifactorial, diverse, intrinsic fetal conditions as well as many maternal and environmental factors. Ultrasonography with color doppler assesmenent remains the only tool for follow-up and diagnosis. Multidisciplinary apporach for assesment, mangement, prevention is imperative. Selective IUGR in monochorionic twins needs attention for optimum perinatal outcome. Future intensive research is desired to establish preventive, diagnostic and therapeutic strategies for IUGR, perhaps affecting the health of future generations.

Keywords: Intrauterine growth restriction, Maternal-fetal risk factors, Screening, Timing for delivery, Selective IUGR, Prevention.

INTRODUCTION

Regulation of fetal growth is multifactorial and complex. Diverse factors, including intrinsic fetal conditions as well as maternal and environmental factors, can lead to intrauterine growth restriction (IUGR). The interaction of these factors governs the partitioning of nutrients and rate of fetal cellular proliferation and maturation.

Although IUGR is probably a physiologic adaptive response to various stimuli, it is associated with distinct short- and long-term morbidities. Immediate morbidities include those associated with prematurity and inadequate nutrient reserve, while childhood morbidities relate to impaired maturation and disrupted organ development. In formulating a comprehensive approach to the management and follow-up of the growth-restricted fetus and infant, physicians should take into consideration the etiology, timing, and severity of IUGR. In addition, they should be cognizant of the immediate perinatal response of the growth-restricted infant as well as the childhood and long-term associated morbidities. A multidisciplinary approach is imperative, including early recognition and obstetrical management of IUGR, assessment of the growth-restricted newborn in the delivery room, possible monitoring in the neonatal intensive care unit, and appropriate pediatric follow-up.

Today we have one single investigating modality, ultrasound and color Doppler, which does accurately assess fetal growth and fetal well-being noninvasively. Most antenatal tests of fetal growth and fetal well-being are principally based on ultrasound techniques and designed to identify the fetuses that are slow growing and fetuses that are in early or late stage of hypoxia and asphyxia. Continuous wave Doppler is employed to provide a continuous trace of fetal heart rate patterns, which get altered with asphyxia. Color and spectral Doppler can identify placental, uterine and fetal vessels and provides information on placental function, uterine perfusion and fetal circulatory response to asphyxia.

Future research is necessary to establish effective preventive, diagnostic, and therapeutic strategies for IUGR, perhaps affecting the health of future generations.

Definitions

Intrauterine growth restriction (IUGR) also refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This functional definition seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes. This definition intentionally excludes fetuses that are small for gestational age (SGA) but are not pathologically small. SGA is defined as growth at the 10th or less percentile for weight of all fetuses at that gestational age. Not all fetuses that are SGA are pathologically growth restricted, and in fact may be constitutionally small. Similarly, not all fetuses that have not met their genetic growth potential are in less than the 10th percentile for estimated fetal weight (EFW).

Of all fetuses at or below the 10th percentile for growth, only approximately 40% are at high risk of potentially preventable perinatal death (Fig. 1), another 40% of these fetuses are constitutionally small. Because this diagnosis may be made with certainty only in neonates, a significant number of fetuses that are healthy but SGA will be subjected to high-risk protocols and, potentially, iatrogenic prematurity.

The remaining 20% of fetuses that are SGA are intrinsically small secondary to a chromosomal or environmental etiology. Examples include fetuses with trisomy 18, cytomegalovirus infection, or fetal alcohol syndrome. These fetuses are unlikely

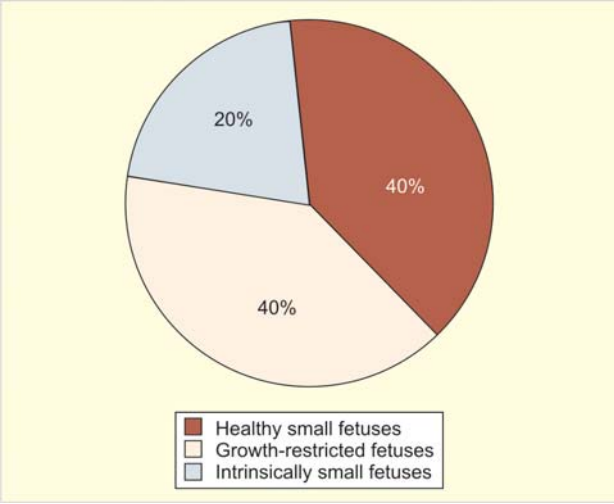


Fig. 1: Risk potential of small for dates fetuses

to benefit from prenatal intervention, and their prognosis is most closely related to the underlying etiology (See Fig. 1).

Pathophysiology

When the hyperplasia and hypertrophy in the second and third trimesters take place in a suboptimal manner it results in deficient growth in the fetal weight, size and maturation of the fetal metabolism, which is called as intrauterine growth restriction (IUGR). Despite vast scientific research done on the topic, the exact definition of IUGR still eludes us. In the most frequently followed definition, emphasis is on the post-delivery weight of the fetus, i.e. < 5 to 10 percentiles of the birth weight along with anthropometric measurements like ponderal index (PI), mid arm circumference (MAC), skin fold thickness, and abdominal and head circumferences (AC, HC). There are many confounding variables like maternal height and weight, race, fetal sex, and birth weight of previous pregnancies, which make the diagnosis of IUGR more difficult.

The clinician's challenge is to identify IUGR fetuses whose health is endangered *in utero* because of a hostile intrauterine environment and to monitor and intervene appropriately. This challenge also includes identifying small but healthy fetuses and avoiding iatrogenic harm to them or their mothers. Some of the terms in relation to growth used are:

- *AGA, appropriate for gestational age*: Birth weight is between 10th and 90th percentile for infant's gestational age (GA).
- *LGA, large for gestational age*: Birth weight > 90th percentile for GA.
- *SGA, small for gestational age*: Birth weight < 10th percentile for GA. Other definitions are sometimes used for SGA, including < 3rd percentile for GA or more than 2 SD below the mean.

IUGR *VS* SGA

IUGR refers to deviation and reduction in expected fetal growth pattern. Multiple adverse conditions inhibit normal fetal growth potential. Not all IUGR infants are SGA. For instance, if the baby was "programmed" to be 4.5 kg at delivery and was only 3.7 kg, it would not be SFD but would be growth retarded and could be expected to have all the problems associated with IUGR.

CLINICAL SIGNIFICANCE AND INCIDENCES

Intrauterine growth restriction (IUGR) affects 3 to 10% of pregnancies; 20% of stillborn infants have IUGR. Perinatal outcome largely depends on birth weight. Infants less than 2,500 gm at term have a perinatal mortality rate 5 to 30 times greater than that of infants whose birth weights are at the 50th percentile. The mortality rate is 70 to100 times higher in infants who weigh less than 1,500 gm. Perinatal mortality rates are 4 to 8 times higher for growth retarded infants, and morbidity is present in 50% of surviving infants. In India, according to recent UNICEF surveys, the incidence of IUGR is 25 to 30%.

ASYMMETRIC *VS* SYMMETRIC GROWTH RETARDATION

Most growth retarded infants have asymmetric growth restriction. First there is restriction of weight and then length with a relative "head sparing" effect. This asymmetric growth is more commonly due to extrinsic influences that affect the fetus later in gestation, such as pre-eclampsia, chronic hypertension, and uterine anomalies. Postnatal growth after IUGR depends on the cause of growth retardation, postnatal nutritional intake, and social environment. Symmetric growth retardation affects all growth parameters. In the human brain, most neurons develop prior to the 18th week of gestation. Early gestational growth retardation would be expected to affect the fetus in a symmetric manner, and thus have permanent neurologic consequences for the infant. Examples of etiologies for symmetric growth retardation include genetic or chromosomal causes, early gestational intrauterine infections (TORCH) and maternal alcohol use.

MATERNAL FETAL RISK FACTORS

Maternal causes of IUGR (adapted from Severi et al 2000) include the following:

- Chronic hypertension
- Pregnancy-associated hypertension
- Cyanotic heart disease
- Class F or higher diabetes
- Hemoglobinopathies
- Autoimmune disease
- Protein-calorie malnutrition
- High pregnancy order/multiparity
- Prepregnancy weight influences fetal size
- Periconceptual nutritional status can affect embryogenesis (e.g. folate deficiency)
- Smoking
- Substance abuse

- Poverty, adolescence, anorexia nervosa, food faddism
- Uterine malformations
- Thrombophilias
- Prolonged high-altitude exposure.

Placental or umbilical cord causes:
- Twin-to-twin transfusion syndrome
- Intrauterine infections (TORCH)
- Placental abnormalities
- Chronic abruption
- Placenta previa
- Abnormal cord insertion
- Cord anomalies
- Multiple gestations.

FETAL CAUSES

The causes of 'true' IUGR are many and include those related to the fetus (e.g. multiple pregnancy, especially monozygous twins) and the mother:
- Medical factors (hypertension, diabetes and immunological disorders, e.g. systemic lupus erythematosus)
- Socioeconomic and nutritional factors
- Drugs including alcohol, tobacco, substance abuse
- Prescription medications (e.g. anticonvulsants, warfarin, steroids), and placental factors, including abnormalities of placental morphology, recurrent abruption/placenta praevia, and immunological disorders affecting the quality of placentation.

A possible association between maternal thrombophilia and IUGR has been postulated but not proven.

There is an increased risk of IUGR in the pregnancies of those women who:
- Were themselves growth restricted at birth
- Have previously had a pregnancy associated with IUGR, and
- Have a sister who has had an IUGR pregnancy.

The recurrence risk was found in one study to be 29% if the first pregnancy was affected, and 44% if two pregnancies have been affected. Recent research has shown that insulin-like growth factor 1 receptor (IGF-1R) gene mutations – leading to disordered function of IGF-1 receptors – may result in restricted intrauterine growth and suboptimal development in postnatal life.

While some maternal risk factors, such as hypertension, abuse of tobacco and other substances, and malnutrition may be amenable to change through healthcare interventions, the problem of IUGR remains difficult to predict or prevent. There is some evidence that treatment induced reductions in maternal blood pressure for women with mild to moderate hypertension may actually adversely affect fetal growth. Similarly, while treatment of significant hypertension in pregnancy is important for protection of the mother, there is no evidence that such treatment improves fetal growth in these pregnancies.

Diagnosis and Surveillance

Criteria for Diagnosis

For most purposes, an EFW at or below the 10th percentile is used to identify fetuses at risk. Importantly, however, understand that this is not a definitive cut-off for uteroplacental insufficiency. A certain number of fetuses at or below the 10th percentile may be constitutionally small. In these cases, short maternal or paternal height, the neonate's ability to maintain growth along a standardized curve, and a lack of other signs of uteroplacental insufficiency (e.g. oligohydramnios, abnormal Doppler findings) can be reassuring to the clinician and parents.

Importantly, review the dating criteria before offering intervention to treat growth restriction in a fetus. If dates are uncertain or unknown, obtaining a second growth assessment over a 2- to 4-week interval is important unless strong supportive data or risk factors warrant an immediate change in management plans.

Screening the Fetus for Growth Restriction

Although no single biometric or Doppler measurements is completely accurate for helping make or exclude the diagnosis of growth restriction, screening for IUGR is important to identify at-risk fetuses. Dependent upon the maternal condition associated with IUGR (see, Maternal causes of IUGR) patients may undergo serial sonography during their pregnancies. An initial scan may be obtained in the middle of the second trimester (at 18-20 weeks) to confirm dates, evaluate for anomalies, and identify multiple gestations. A repeat scan may be scheduled at 28 to 32 weeks' gestation to assess fetal growth, evidence of asymmetry, and stigmata of brain-sparing physiology (e.g. oligohydramnios, abnormal Doppler findings).

Screening for IUGR in the general population relies on symphysis – fundal height measurements. This is a routine portion of prenatal care from 20 weeks until term. Although recent studies have questioned the accuracy of fundal height measurements, particularly in obese patients, a discrepancy of greater than 3 cm between observed and expected measurements may prompt a growth evaluation using ultrasound (Jelks et al). The clinician should be aware that the sensitivity of fundal height measurement is limited, and he or she should maintain a heightened awareness for potential growth-restricted fetuses. In an unselected hospital population, only 26% of fetuses, SGA, were suggested to be SGA based on clinical examination findings.

One study using fundal height curves that customized for maternal weight, height, and ethnicity was able to increase the detection rate from 29.2% in the control group to 47.9% in the study population. As Yoshida et al indicated, these inaccuracies occur:
- Because of the limited accuracy of predicting birth weight within 10% using ultrasonography in the third trimester,
- Because not all fetuses that are SGA have IUGR,

- Because individual and unpredictable changes in growth potential occur, and
- Because growth distribution is a continuum.

Diagnostic and Assessment Tools for Evaluation of IUGR (Table 1)

Management of IUGR

The goal in the management of IUGR, as no effective treatments are known, is to deliver the most mature fetus in the best physiological condition possible while minimizing the risk to the mother. Such a goal requires the use of antenatal testing with the hope of identifying the fetus with IUGR before it becomes acidotic. Developing a testing scheme (Flow Chart 1) following it, and having a high index of suspicion in this population when results of testing are abnormal is important. The positive predictive (as for end diastolic flow, Flow Chart 2) value of an abnormal antenatal test result in fetuses with IUGR is relatively high because the prevalence of acidemia and chronic hypoxemia is relatively high.

The basic steps in management of IUGR consist of:

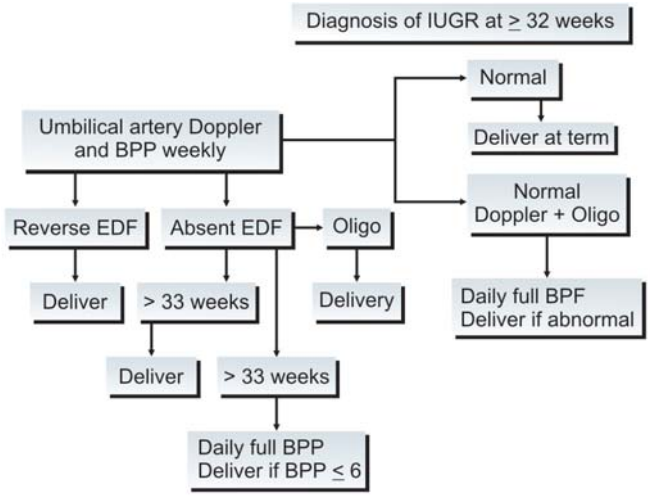
- Early and reliable diagnosis of IUGR
- Close antenatal monitoring, amelioration of causative pathology (if identified), therapy to prevent IUGR
- Optimum timing, mode of delivery, intrapartum management
- Neonatal management
- Prevention/reduction of IUGR in subsequent pregnancies.

Table 1: Diagnostic and assessment tools relating to IUGR

Screening
- Biochemical
  - alpha-fetoprotein
    it ↑ in absence of fetal anomaly, risk of IUGR later in pregnancy is ↑ 5-10X
- Clinical
  - palpation
  - SFH measurement (customized)
- Ultrasound
  - HC
  - AC
  - EFW
    < 10th percentile on customized charts or reduced growth velocity indicate IUGR

Confirmation of diagnosis
- Ultrasound
  - fetal/placental morphology
  - UA Doppler
  - ± assess of TORCH infections
  - ± fetal karyotyping

Monitoring of IUGR affected pregnancy
- Ultrasound
  - UA Doppler
    ± MCA Doppler
    ± Fetal venous studies
  - AFI
  - ± BPP
- ± cordocentesis (rarely)



Flow Chart 1: BPP–biophysical profile; EDF–end diastolic flow; IUGR–intrauterine growth restriction

STEPS OF MANAGEMENT

Accurate dating is essential for making the diagnosis of IUGR. The best parameter for reliable dating is a sure date for the last menstrual period in a woman with regular cycles. The alternative is assessment by an ultrasound examination performed from 8 to 13 weeks of gestation. Ultrasound dating is only accurate to about 3 weeks when it is performed at term. An error commonly made is to change a patient's due date on the basis of a 3rd trimester ultrasound. Doing so can result in failure to recognize IUGR.

General Lines

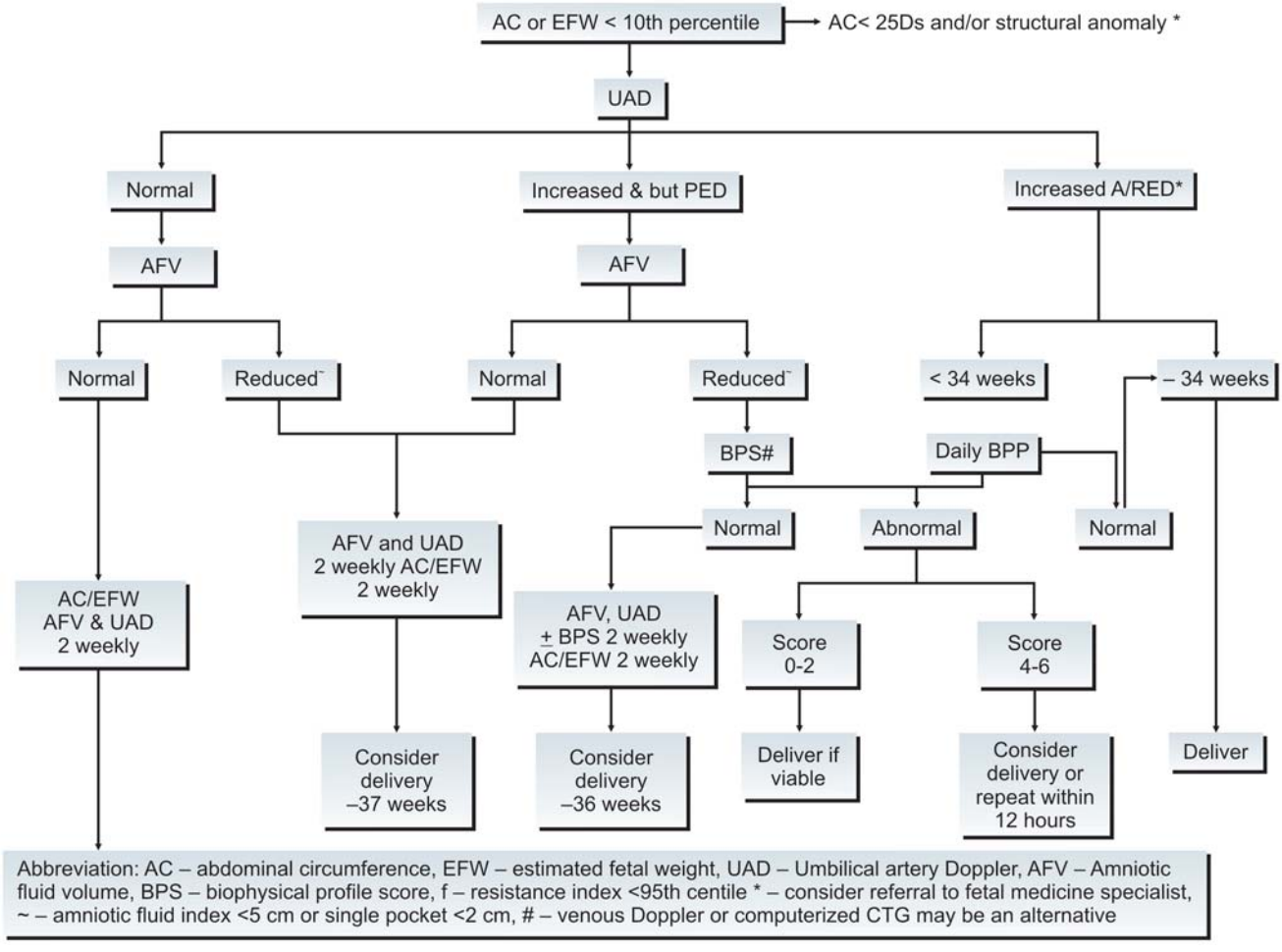
- Treat any maternal disease
- Stop smoking and substance abuse
- Improve maternal nutrition
- Advise more bed rest.

Tests to Assess Fetal Well-being and Growth

- Daily fetal movement count
- Growth scans every 3 weeks
- Ultrasonographic assessment of the amount of amniotic fluid
- Non stress test: Frequency varies from once, weekly to daily testing
- A CST or biophysical profile is used as backup tests.

Timing of Delivery

- At 34 weeks or more: If tests for fetal well-being are normal and fetal growth is adequate, continue fetal surveillance and deliver at term.
- At less then 34 weeks: If no fetal growth is noted or severe oligohydramnios is detected, assess fetal lung maturity. Deliver if lungs are mature.



Flow Chart 2: Management algorithm for small gestational fetus

- Otherwise, administer corticosteroids to enhance fetal lung maturity and reassess.
- Delivery is mandatory if tests for fetal well-being is abnormal.
- Delivery is indicated at any time if the end diastolic flow is absent or reversed and other surveillance is abnormal.
- Delivery is also indicated in the presence of absent/reversed flow regardless of biophysical tests at a gestational age of 34 weeks or more.

Labor and Delivery

- Delivery should be in a well-equipped hospital with neonatal IC facilities.
- Administer epidural analgesia.
- During first stage of labor, continuous EFM is performed.
- Try amnioinfusion in cases of nonreassuring fetal heart rate, low amniotic fluid index and meconium stained liquor.
- Use ventouse or forceps to minimize 2nd stage. CS is indicated whenever there is evidence for deteriorating fetal status.
- Instruct the patient regarding adequate technique for bearing down.
- Examine the placenta by a pathologist to identify the cause.

Prognosis

- The worst is for IUGR due to congenital infections or chromosomal abnormalities.
- IUGR babies suffering intrapartum asphyxia are more likely to suffer neurologic problems at childhood compared to AGA babies.
- The length of the insult is more important than its severity in terms of somatic growth and neurologic development.
- The probability of developmental problems is lower when there is a catch-up growth during the first 6 months of life.

Selective Intrauterine Growth Restriction (SIUGR)

Although most pregnancies with selective intrauterine growth restriction (SIUGR), also called monochorionic twins (twins that share a common placenta) are uncomplicated, the presence of a common placenta does pose a relatively increased risk to the welfare of the fetuses. The single placenta contains blood vessels that link the blood flow between the twins. Unbalanced flow of blood from one twin to the other twin may lead to a cascade of events that result in twin-twin transfusion syndrome. Another potential problem that may occur in monochorionic twins is the disproportionate distribution of placental mass

between the twins. This factor may result in poor nourishment of one of the twins resulting in subsequent poor overall fetal growth. Because this problem typically affects only one of the fetuses, this condition has been coined selective intrauterine growth restriction (SIUGR). SIUGR is estimated to occur in approximately 10% of monochorionic twin pregnancies.

Severe cases of monochorionic twins with SIUGR show ultrasound evidence of abnormal blood flow through the umbilical artery of the poorly grown twin. In this circumstance, spontaneous death of this baby within the womb may occur in upto 40% of cases. Because of the blood vessels that link the twins' circulatory system together, death of one twin may result in severe drop in blood pressure of the other twin and subsequent brain damage (up to 30%) or death (up to 40%). This complication results from the hemorrhage of blood from the appropriately grown twin into the demised SIUGR twin.

Because the adverse effects to the appropriately grown twin is mediated through the blood vessels that link the circulations of the twins, it has been suggested that obliteration of these vascular communications may result in improved outcomes for the normally grown twin. Separation of the circulations may be done using the surgical techniques, which were originally developed for the treatment of twin-twin transfusion syndrome. Laser therapy promises good results.

Future Directions and Prevention

Prevention of IUGR is highly desirable, and several studies have addressed this potential. Investigators have looked at altering the thromboxane-to-prostacyclin ratio by administering aspirin with or without dipyridamole to mothers of fetuses with IUGR. The studies examining these agents for prevention of IUGR are difficult to compare. Different doses of aspirin, different times of administration in pregnancy, and different indications for definitive clinical use. However, some factors may increase the risks of IUGR, such as cigarette smoking and poor maternal nutrition. Avoiding harmful lifestyles, eating a healthy diet, and getting prenatal care may help decrease the risks for IUGR. Early detection may also help with IUGR treatment and outcome.

CONCLUSION

IUGR remains a challenging problem for clinicians. Most cases of IUGR occur in pregnancies in which no risk factors are present; therefore, the clinician must be alert to the possibility of a growth disturbance in all pregnancies. No single measurement helps secure the diagnosis, thus a complex strategy for diagnosis and assessment is necessary. The ability to diagnose the disorder and understand its pathophysiology still outpaces the ability to prevent or treat its complications. The current therapeutic goals are to optimize the timing of delivery to minimize hypoxemia and maximize gestational age and maternal outcome. Further study may elucidate preventive or treatment strategies to assist the growth-restricted fetus.

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