REVIEW ARTICLE

Ultrasound and Doppler Management of Intrauterine Growth Restriction

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Abstract

Review of present knowledge about fetal growth, and clinical and ultrasonography diagnosis of Intrauterine growth restriction by means of 2D and 3D. The review included the diagnosis of type of IUGR and the study of fetal deterioration (Chronic Tests and Acute Markers). Also the obstetrics management.

Keywords: Intrauterine growth restriction, Fetal biometry, Ultrasonography, Doppler.

INTRODUCTION

Intrauterine growth restriction (IUGR) undoubtedly is one of the most challenging areas of research for obstetricians today. It is considered a major contributor to perinatal morbidity and mortality, and has been described as etiologically responsible of about a 50% of perinatal deaths occurring preterm and 20% at term.[1] In addition, growth restriction is associated with intrapartum distress and metabolic acidosis, which are in turn contributors to hypoxic encephalopathy and cerebral palsy.[2] Furthermore, there is increasing evidence of the association between fetal growth restriction and infant death[3] and metabolic syndrome in adulthood.[4] Despite marked progress made over the past two decades in both diagnostic procedures and management strategies, the question of what causes growth restriction still remains unanswered in 30-40% of all cases of IUGR.

DEFINITIONS

It is necessary to make a difference between three different concepts: growth, development and maturity. 'Growth' is usually defined as the process whereby the body mass of a living being increases in size as a result of the increase in number and or size of its cells. 'Development', should be understood as the process by which the organs acquire their particular anatomy and their specific functions in living beings, and consequently the progressive anatomical and functional 'Maturity' of all them, as well as its physiological regulations. Thanks to these three processes, that are going on in a parallel way, the fetus reach at the gestation terminus maturity enough to face the extrauterine life.

Regarding to the fetal weight anomalies, a clear distinction should be made between the meanings of three different terms: Low birth weight (LBW), Small-for-gestational age (SGA), and Intrauterine growth (IUGR). LBW refers only to newborn infants weighing less than 2500 gm independently of gestational age. Some of these newborns will be premature, and others will be newborns with a growth restriction. SGA is a term based on a statistical definition, which includes all newborn infants found below the lower range limit of normal weight by gestational age. Hence, is a term that comprises an heterogeneous group of fetuses and newborns with a several etiologic conditions. IUGR theoretically refers to any process that is capable of limiting intrinsic fetal growth potential "*in utero*", but is mainly used to define those cases in which a placental insufficiency is responsible for the growth deficit.

Unfortunately, in literature, the terms IUGR and SGA are frequently considered as synonymous. This confusion was increased even more when the National Institute of Child Health and Human Development in the USA stated that for "both medical and research purposes, IUGR should be defined as a situation which results in a newborn weight that is lower than 10th percentile for its gestational age".

CLASSIFICATION

Most fetal medicine units classify SGA in three main categories according to what Soothill published in a breaking

editorial.[5] Firstly, the 'IUGR', that is limited to those fetuses in which a reduction in their growth potential is believed to be due to placental insufficiency. Secondly, the 'Normal-SGA', which includes those SGA fetuses which are believed to be constitutionally small. And, finally, the 'Abnormal-SGA', which comprises other pathological causes of SGA as infections, congenital malformations, cromosomopatias, etc. Despite that in the past SGA fetuses and neonates were classified according to the relationship between abdominal and cephalic biometries as symmetrical or asymmetrical, this classification has demonstrated to be poorly correlated with the underlying ethological condition,[6] with the gasometric status of the fetus at cordocentesis[7] or with any of the perinatal events that define an adverse perinatal outcome,[8,9] and, therefore, is no longer recommended as a primary tool in managing SGA fetuses.

INCIDENCE

While the incidence of SGA depends upon the used threshold for normality (10th, 5th or 2.5th centile) resulting in a 10%, 5% or 2.5%, respectively, the incidence of IUGR varies greatly in the literature, with reports of figures ranging from 1 to 12%. The reason for this may be found in different factors, including the social and economic status of the population studied, different criteria used for discrimination (10th percentile, 5th percentile, etc.), different ways in which standard curves are drawn, data obtained from transverse or longitudinal studies, etc.[10] Approximately, only a 20-30% of all SGA fetuses are true growth-restricted fetuses,[11] whereas only a 10-20% are pathological-SGA.[12] Hence, most cases of SGA are constitutionally small, i.e normal-SGA.

SCREENING

´Traditional´ maternal serum screening have proved disappointing for IUGR: elevated levels of alphafetoprotein and human chorionic gonadotrophin are associated with IUGR but are very poor screening tests (sensitivity about 5%).[13] For the time being, the biochemical markers that are more promising candidates for antenatal screening are fms-like tyrosine kinase 1 and placental growth factor. Despite that it exists evidence of the association between the plasmatic maternal levels of these markers and the occurrence of preeclampsia and growth-restriction,[14] new clinical studies are required before its clinical application.

Since IUGR is caused by utero-placental insufficiency, and it shares some common physiopathological paths with preeclampsia leading to a poor trophoblast invasion, IUGR has been associated with an increased resistance in the uterine arteries. Doppler evaluation of this vessel constitutes the main screening method for IUGR. Evaluation of this tool has been hampered by different criteria for growth-restricion and for abnormal Doppler waveform, by discrepancies in the targeted population and by differences in instrumentation (use of color Doppler, transvaginal *vs* transabdominal approach) among the studies. Nevertheless, a multicentric and massive-population-based study[15] aimed to evaluate the role of transvaginal uterine artery at 23 weeks, has demonstrated an overall sensitivity for growth-restriction of 16%. Nevertheless, when the event of interest is the occurrence of disease requiring delivery before 32 weeks (which represents the subgroup with significant perinatal morbidity and mortality), the sensitivity for preeclamsia-associated and no-preeclamsia associated growth restriction is 93 and 56%, respectively, with specificities of 95%. It would be appealing to move the screening into early pregnancy, but despite the fact that it seems a promising strategy for preeclampsia, the sensitivy of uterine artery Doppler evaluation in early second trimester for growth restriction requiring delivery before 32 is only of 28% (12% for growth restriction without preeclampsia).[16] Hence, it seems that uterine artery evaluation identifies a subgroup with an increased risk for developing severe growth-restriction.

Screening strategies which combine epidemiological, biochemical and Doppler parameters are being tested to enhance the low sensitivity of each individual parameter.

DIAGNOSIS

The antenatal detection of IUGR is of utmost importance and constitutes a major challenge for modern obstetrics. SGA neonates not antenatally detected had a 4-fold risk of adverse outcome.[17] Furthermore, it has been reported that a suboptimal antenatal management is the most common finding in cases of unexplained stillborns[18] (Fig. 1).

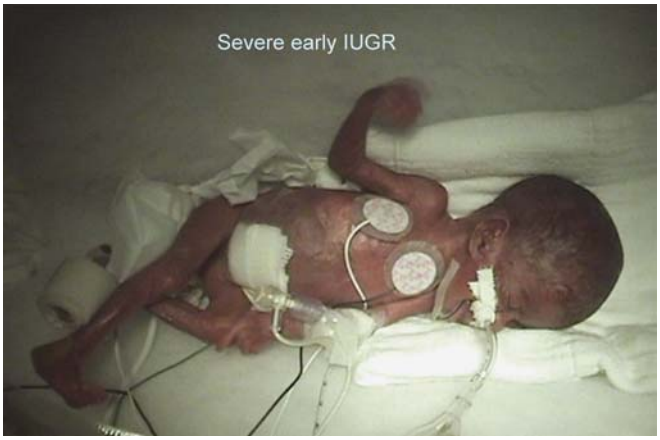

Fig. 1: Severe early IUGR delivered after deterioration of fetal Doppler parameters

Anamnesis

Antenatal risk factors include a previous history of SGA or stillbirth, toxics such as tobacco, alcohol and other drugs, fetal infections (CMV and Rubeola are the most associated ones) and maternal diseases (mainly renal and vascular). Other risk factors are preeclampsia related, such as thrombophilic conditions, obesity, and chronic hypertension. Although these risk factors are multiple and not always well defined, a correct anamnesis remains a key step to select a population of high-risk on which a close follow-up may be warranted. Nevertheless, only 10% of this high-risk group will develop IUGR.

Fundal Height Measurement

Both the fundal height measurement and the abdominal palpation have sensitivities of about 30% to detect SGA[19] and, therefore, could not be recommended. Nevertheless, it has been reported that customized standards for fundal height, which adjust for parity, maternal height and weight, ethnicity and fetal gender, and a longitudinal evaluation allow sensitivities of about 50%,[20] comparable to the detection rate of routine third trimester fetal biometry in low-risk pregnancies. In settings where a policy of third trimester ultrasound is not in place, fundal height measurements remain common practice.

Ultrasound Diagnosis

An accurate antenatal detection of SGA fetuses remains the key process to subsequently detect and manage IUGR. This ultrasound assessment require three consecutive steps: (i) pregnancy dating; (ii) biometric evaluation; and, (iii) assessing growth as normal or abnormal.

Pregnancy Dating

Pregnancy dating based upon the last menstrual period provides inaccurate estimates of the gestational age, since up to a 20% of women with regular cycles ovulate later than expected[21] (Fig. 2).

Hence, in clinical settings where a policy of first or early second trimester scan is in place, it seems to be more appropriate to systematically use the fetal biometries to date the pregnancy and ensure a reliable fetal age assesment for most purposes, for example Down's syndrome screening. There are several formulae to date the pregnancy from early biometries, with low systematic and random errors. Crown-rump length (CRL) is a biometric parameter that can be measured in the early stages of gestation (Fig. 3).

Technically the main limitation is the progressive bending of the embryo which makes measurements less

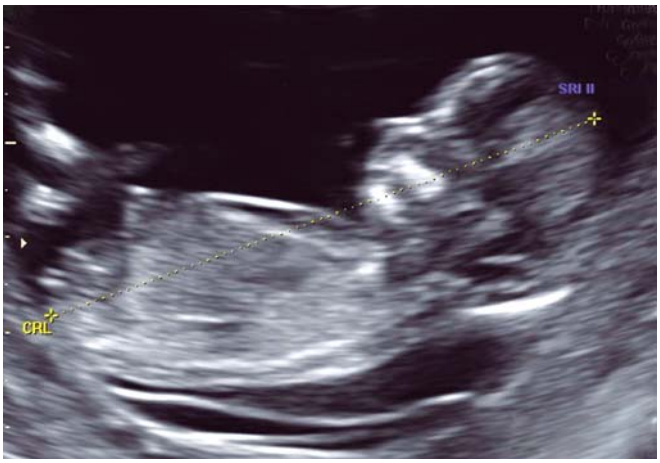

Fig. 2: First trimester screening pregnancy dating. Trisomia 21, CRL, present nasal bone

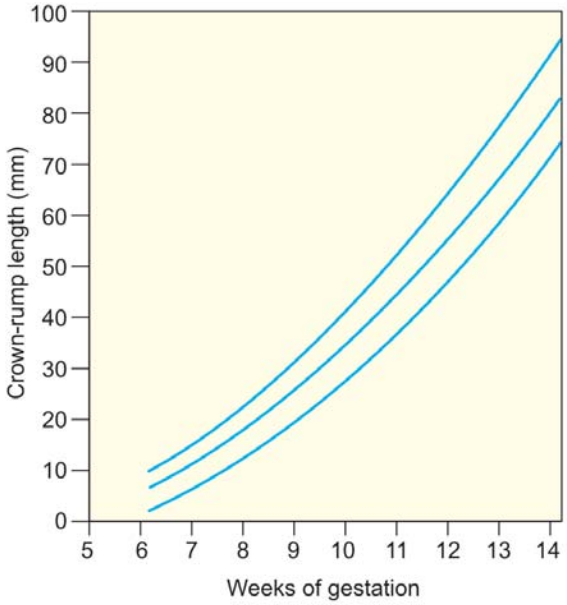

Fig. 3: Mean +/– 2 SD fetal crown-rump lenght for gestational age (6-14 weeks)

reliable beyond 12-13 weeks of gestation (or 60-70 mm). Normal reference ranges to date the pregnancy are published elsewhere.[22] If possible, below the 14 weeks, all obstetric ultrasound units are currently recommended to adopt this method of assessing gestational age from crown rump length. From then on, it seems conceptually more appropriate to use cephalic (head circumference) and/or femur (femur length) biometries. Series in which different formulas have been tested in pregnancies conceived with artificial reproductive techniques provide comprehensive recommendations on this matter.[23] Once the pregnancy has been dated by an early scan, further adjustments must not be performed.

Biometric Evaluation

Initially, and still in many places, the biparietal diameter (BPD) was the only measurement that was routinely taken for the assessment of fetal growth. When pregnancy is normal, this parameter falls within the normal range and can be consider a representative indicator of the growth of other fetal organs and tissues, but when pregnancy is abnormal it may still fall within the normal range (head size is rarely affected in many cases of IUGR) although in this case it is not representative indicator of the growth of other fetal structures. On the other hand, misdiagnoses have been on many occasions in fetuses with marked brachycephalism or dolichocephalism in association with normal development of the rest of the body. In addition, measurement of the BPD does not permit determination of fetal weight with acceptable reliability. The substitution of BPD by head circumference or cephalic area does not substantially improve the sensitivity of the method. With the purpose of improving the screening method, measurement of the length of the femur was introduced. It has the advantage that it measures a component of fetal longitudinal growth and does not suffer the sudden flattening out characteristic of cephalic parameters at term, although it has the disadvantage of not being a useful parameter for establishing the diagnosis of IUGR early stages. Abdominal circumference (AC) is the most accurate single biometry to predict SGA at birth[24] (Fig. 4).

In high-risk women, AC at less than the tenth centile has sensitivities of 72.9-94.5% and specificities of 50.6-83.8% in the prediction of fetuses with birthweight at less than the tenth centile. The use of cross-sectional reference charts for each biometry with the closest distribution to that of the screened population remains the gold standard and some studies alert to the impact of choice of reference charts in the assessment of fetal biometry. In that sense they recommend to use Z-scores in order to choose the most appropriate chart.[25] Moreover, many charts require the average of at least three repeat measurements in order to control random error. By increasing the number of measurements to four, the 95% error span is reduced to half.

Fetal biometries could be used to estimate the fetal weight. The estimated fetal weight (EFW) predicts the occurrence of SGA at birth with sensitivities of 33.3-89.2% and specificities of 53.7-90.9%.[24] A prospective study[26] comparing several formulas concluded that Shepard formula[27] have the best interclass correlation coefficient, with smallest mean difference from actual birthweight. Nevertheless, for fetuses weighting less than 2000 gm, this formula has not been validated. The Hadlock formula[28] may be more appropriate when the fetus is expected to be very small.[29]

Controversy exists regarding using AC or EFW for the antenatal assessment of fetal growth. Whereas AC, the simplest method, has in high-pregnancies higher sensitivities, EFW has a stronger association with birthweight below the 10th centile.[24] We prefer using EFW since is more consistent with the neonatal assessment, which is mainly performed by weight. In addition, the accuracy of the individual fetal parameters cannot be checked as there is no gold standard. On the contrary, estimated fetal weight could be assessed against birthweight and has a random error of about 8%.[28]

Since growth is a dynamic process, it seems logical that its quantification requires the evaluation of serial measurements. In fact, serial measurements of AC and EFW are superior to single estimates in the prediction of neonatal growth restriction defined by ponderal index or skinfold thickness[30] (Fig. 5) and in the prediction of adverse outcome.[31]

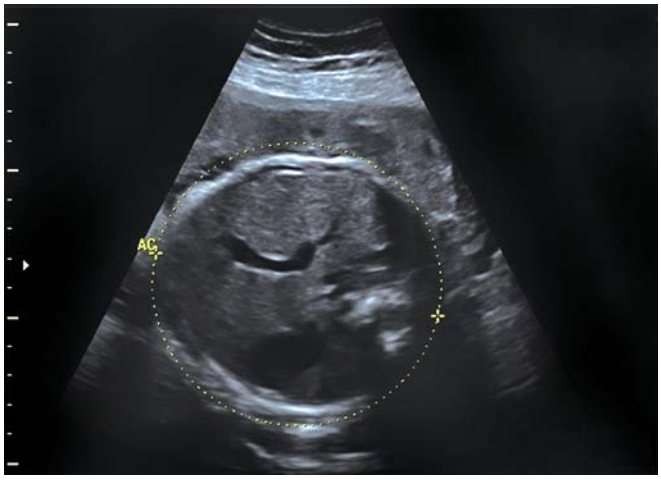

Fig. 4: Abdominal circumference in a case of IUGR and intrahepatic cholestasis in pregnancy

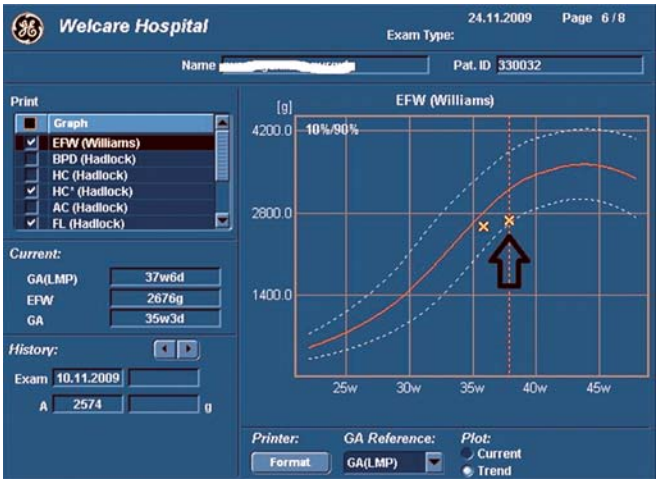

Fig. 5: Serial biometrical measurements, approaching 10th centile in a case of IUGR with intrahepatic cholestasis in pregnancy

Nevertheless, from our point of view there are major concerns regarding the use of serial measurements. Firstly, there is a scarcity of published normal ranges for growth velocity and is common practice to use normal ranges derived form transversal series to evaluate serial measurements, and use of standards across population may be misleading. Secondly, there is no agreement regarding the optimal methodology. Theoretically, conditional centiles, whereby the EFW or AC of each individual fetus at a first ultrasound examination is extrapolated to give a range of normal ranges (expressed as centiles) at a later scan, appears to be the most appropriate method for longitudinal growth assessment.[32] Compared to the ranges for the entire population, the conditional ranges for small fetus would be narrower and skewed in the direction of the initial measurement.[33] However, this approach has not demonstrated to be superior to other methodologically more straightforward alternatives, such as z-velocity.[34] In addition, the interval between scan is of paramount importance since 2-week intervals are associated with false-positive rates for growth restriction in excess of 10%, increasing to much higher rates late in the third trimester.[35] A 4-week interval, which is a too long interval for clinical purposes in high-risk pregnancies, has been reported to optimize the prediction.[36]

Individualized growth standards could be inferred in a forward direction on the basis of ultrasound biometry in early pregnancy. The Rossavik model[37] calculates an expected growth curve from two scans at about 18 and 24-26 weeks. In addition to have failed to demonstrate an improvement in the prediction of fetal weight,[38] there are several concerns regarding it conceptual framework. First, ultrasound error at each of the sequential scans can lead to substantial variation when forward projecting the growth curve that has been calculated from these measurements. Second, the fetus could already be affected by early-onset growth restriction, especially at the latter of the two scans, which would result in depressed values being projected as a "norm".

Assessing Growth

The normal ranges used when evaluating fetal growth is a question of utmost importance. When evaluating single measurements, such as AC, it is recommended to use local standards since differences between populations could be a source of unaccuracy. Nevertheless, strict methodological requirements are needed for normal ranges: a transversal design (each fetus is measured only once), reliable dating, enough sample size at the extremes of the gestational age and correct exclusion criteria. With regard to the question of selection criteria for the development of fetal size, only conditions for which information is available at the time of scanning for fetal growth should be excluded, such as fetal malformations and maternal diseases frequently associated with IUGR.[39] A comprehensive review of several reference range is provided elsewhere.[40]

For AC, a systematic review[24] found that a threshold of the tenth centile had better sensitivities and specificities than other commonly used centiles.

Regarding normal ranges for fetal weight, neonatal weight is frequently used as a proxy for fetal weight. Nevertheless, due to the fact that an epidemiological association exist between IUGR and preterm delivery exists, the birthweight distribution in preterm gestations is negatively skewed, while the distribution of fetal weight at the same gestation is close to normal.[41] As a consequence, population-based standards fail to identify a significant proportion of cases of preterm intrauterine SGA.[42]

For EFW, a systematic review[24] found that a threshold of the tenth centile had better sensitivities and specificities than other commonly used centiles.

Due to the fact that several maternal (height, weight, race, age, parity,…) and fetal (number, gender,…) variables play a significant role in fetal growth both in low and high risk pregnancies, population-based birthweight standards result in misclassification of a large proportion of cases.[43] Individually adjusted or customized growth charts aim to optimize the assessment of fetal growth by taking individual variation into account, and by projecting an optimal curve which delineates the potential weight gain in each pregnancy. The use of customised birthweight standards, which take these factors into account, has demonstrated to improve the definition of SGA and the prediction of abnormal 5-minute Apgar score, hospital stay length, admission to the intensive care unit, hypoglycemia, need for neonatal resuscitation and perinatal death, both in high-risk[44] and low-risk[45-48] populations. On the other hand, those neonates with a normal customized birthweight have been found to have a perinatal outcome comparable to the general population, regardless of being SGA according population-based centiles.[44-47] The inference of these findings is that SGA according to customized standards and growth restriction are equivalent, and it has been claimed that customized SGA could be used as reliable proxy of growth restriction.[43]

Regarding the customized fetal weight assessment, it has been found that a threshold of the tenth centile had better sensitivities and specificities than other used centiles for the prediction of adverse outcome.[44]

Three-dimensional Fetal Growth Assessment

The advent of three-dimensional sonography has allowed a new insight into fetal growth. The upper arm[49] or thigh[50] volumes are parameters for detecting IUGR,[46] but need further validation. Calculation of organ volumes could also be made reliably and in a non-invasive way using this new technology. Interestingly, the fetal brain/liver volume ratio has been described[51] as a predictor of fetal outcome in the growth-restricted fetus. An inverse relationship exists in small-for-gestational-age fetuses between brain/liver volume ratio and fetal weight-related umbilical venous blood flow. The benefit of prospectively assessing organ values also requires further studies and could not be recommended.

DIAGNOSIS OF THE TYPE OF SGA

Following the diagnosis of a SGA fetus, further evaluation is warranted to determine the type of SGA.

Abnormal-SGA

i. *Anatomical ultrasound*: An anatomical study is mandatory to rule out the presence of malformations (up to 25% of malformed fetuses are SGA) or the presence of signs of fetal infection (ventriculomegaly, microcephalia, brain or intraabdominal calcifications, placentomegaly, hydramnios, ...). Most cases of congenital cytomegalovirus infection have oligohydramnios, and therefore should be considered in the differential diagnosis.

ii. *Karyotyping*: Up to 15% of the abnormal SGA fetuses have some associated syndrome,[47] being either aneuploidy, nonaneuploid syndromes. Some of them are recognized to be related to imprinting/methylation defects, as for example the Silver Rusell, a clinically heterogeneous syndrome characterized by intrauterine and postnatal growth retardation with spared cranial growth, dysmorphic features and frequent body asymmetry. The risk of association is greater when there are associated structural abnormalities, a normal liquor volume or a normal uterine or umbilical artery Doppler. Therefore, it may also be appropriate to offer some genetic studies in selected cases.

iii. *Infectious study*: Although less than the 5% of the cases are associated with infection, a TORCH serology seems reasonable to rule out this etiology. In most developed countries, the most prevalent infectious etiology of SGA is the cytomegalovirus. In cases in which an early infection is suspected, an amniotic fluid PCR determination for cytomegalovirus may be useful even in the presence of a negative maternal IgM.

IUGR versus Normal-SGA

The differentiation between growth-restricted and constitutionally small fetuses is essential for clinical practice: whereas the former are those who have failed to reach its genetically endowed growth potential, the latter are considered to represent one end of the normal size spectrum. The benchmark for this differentiation is the Doppler evaluation.

i. *Umbilical artery doppler*: Vasoconstriction phenomena of the tertiary stem villi[52] are considered responsible for the up river modifications in the normal wave flow velocity of the umbilical artery with a decrease in the diastolic velocities and an increase in the resistance and impedance indices. From the pioneering research in Doppler it has been clearly demonstrated that abnormal umbilical Doppler correlates with histological evidence of placental vascular pathology (Fig. 6).

As a result, Doppler umbilical artery indices correlate with fetal levels of glucose, aminoacids and blood gases[53,54] (Fig. 7) and therefore, it could be considered a surrogate measurement of the placental functionality.

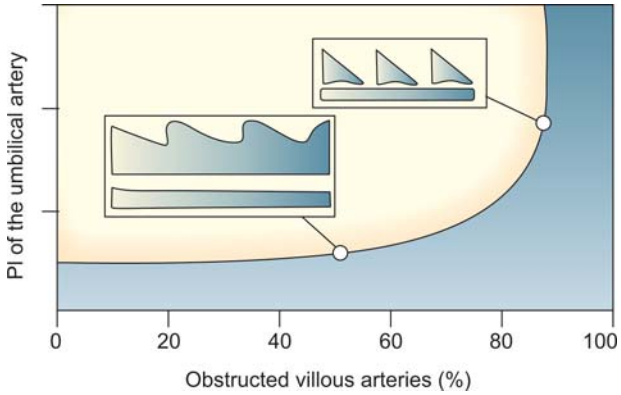

Fig. 6: Trudinger mathematical model,[55] relating the morphologie of the flow velocity waveform of the umbilical artery (Doppler) with the resistance in the villous arteriolar system (percentage of obstructed villous arteries)

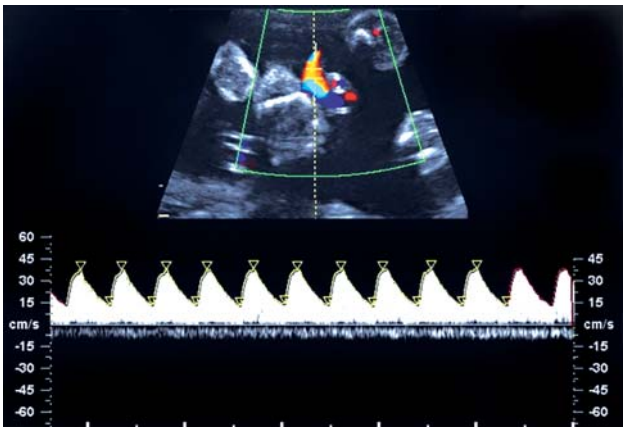

Fig. 7: Spectral Doppler. Umbilical artery. Free loop

Moreover, a decreased flow in the umbilical vein has also been demonstrated in an as symptomatic stage of the disease related to a decrease of the placental volume. SGA with abnormal umbilical artery Doppler are more severely small.[55-57] There is an extensive body of evidence that those SGA fetuses with abnormal umbilical artery flow are at higher risk of adverse perinatal outcome than those with normal flow.[31,45,55-60] Even when controlling for gestational age at delivery some series have reported a significant association between abnormal umbilical artery flow and the perinatal results.[31,55,60] In addition, the occurrence of perinatal death in the presence of a normal umbilical flow is very uncommon.[55,57,61] Thus, Doppler of the umbilical artery flow could be considered a risk-discriminator tool in the management of SGA fetuses. Evidence supports those SGA fetuses with normal Doppler benefit from a non-intensive follow-up.[62] As a consequence of this evidence, SGA fetuses with normal Doppler have been claimed normal SGA fetuses, representing the lowest spectrum of healthy fetuses and to manage them accordingly.[63,64] Some recent studies would suggest that even those normal-SGA would have a suboptimal perinatal and neuro-developmental outcome,[65,66] suggesting that a proportion of these SGA fetuses are, in reality, late-onset mild IUGR cases.

ii. *Cerebroumbilical ratio:* It has been claimed that the relationship between the umbilical and cerebral flow provides a more sensitive tool to discriminate between constitutional SGA and IUGR as it may be decreased even when UA and MCA are very close to normal. In fact, animal models have demonstrated that this ratio is better correlated with hypoxia than its individual components[62,67] (Fig. 8).

Furthermore, it has also been extensively reported that the prediction of adverse outcome is improved using umbilical and cerebral parameters in a combined

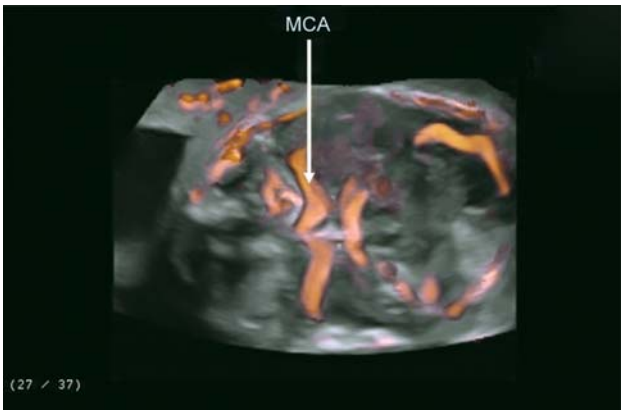

Fig. 8: Circulus arteriosus Willisii with middle cerebral artery (MCA) 3D power Doppler

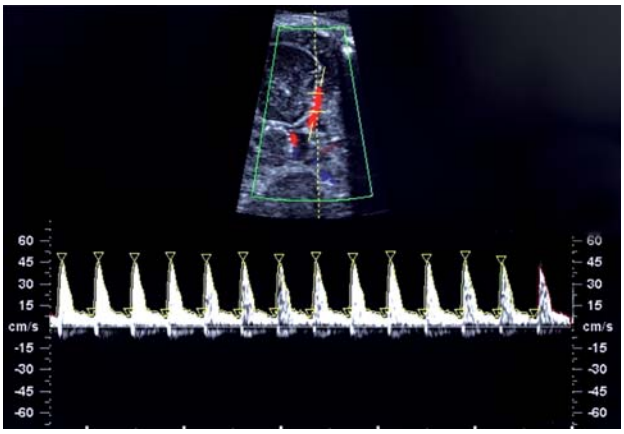

Fig. 9: Circulus arteriosus Willisii. Normal ACM spectral Doppler signature with typical high resistance for early 3rd trim

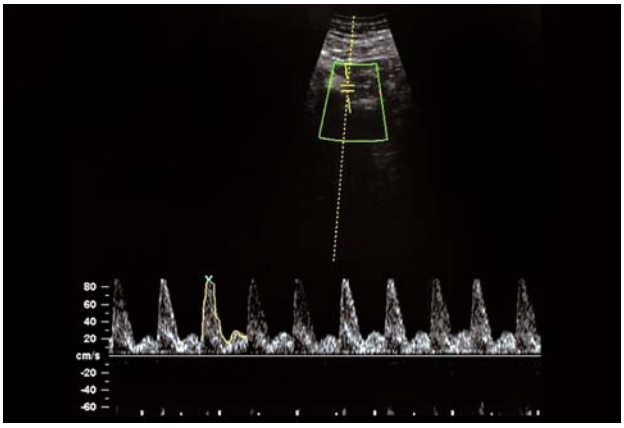

Fig. 10: IUGR uterine artery spectral Doppler with increased pulsatility index and notching

ratio,[68-74] with sensitivities of about 70%[64,69,75] (Fig. 9). This initial redistribution would also be reflected in an impaired flow in the fetal aorta.

iii. *Uterine artery*: A defective trophoblast invasion is a common pattern in early and severe cases of growth restriction[76] (Fig. 10), and this phenomenon is responsible for the presence of abnormal flow patterns in the uterine artery.

It has been suggested that uterine artery Doppler provide additional value to the umbilical and cerebral arteries to predict the occurrence of adverse outcome media,[77,78] and some management protocols consider this parameter as a criteria for IUGR independently to the fetal Doppler parameters. Nevertheless, a systematic review with meta-analysis[79] found that uterine artery Doppler had limited accuracy in predicting IUGR and perinatal death, and, therefore, its use needs to be evaluated further in studies.

STUDY OF FETAL DETERIORATION

Assessment of fetal well-being and delivery when the risks of leaving the fetus in an intrauterine hostile environment

are considered to be greater than the risks of prematurity remains the main management strategy for IUGR fetuses. Fetal well-being tests could be classified as chronic or acute. Whilst the former become progressively abnormal due to increasing hypoxemia and/or hypoxia, the later correlate with acute changes occurring in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis, and usually precede fetal death in few days. Since it does not exist a fixed sequence of fetal deterioration, integration of several well-being test into comprehensive managements protocols seems to be warranted.

Chronic Tests

Umbilical Artery

Vasoconstriction changes of the tertiary stem villi[52] (Fig. 11) are considered responsible for the up river modifications in the wave flow velocity of the umbilical artery with a decrease in the diastolic velocities and an increase in the resistance and impedance indices.

In advanced stages of placental histological and functional damage, diastolic velocities will become absent or even reversed. It has not been demonstrated qualitative differences in placental histological changes between cases of IUGR with abnormal but positive diastolic flow and cases with reversed end-diastolic flow,[52] and, therefore, the later is considered the end of the spectrum of placental damage and is associated with an increased risk of perinatal death. As suggested by animal[80] and mathematical[81] experimental models of chronic placental embolization, it is required the obliteration of more than a 50% of the placental vessels before absent or reversed end-diastolic velocities appear.

Studies where IUGR fetuses were followed longitudinally[82] have reported that up to 80% of the fetuses have abnormal umbilical artery indices 2 weeks before the fetal acute deterioration, and, therefore, this parameter could be considered a chronic marker. End-diastolic velocities have been reported to be present on average 1 weeks before the acute deterioration.[82] Up to 40% of fetuses with acidosis shows this umbilical flow pattern.[82] Despite the fact that an association exist between the presence of reversed end-diastolic flow in the umbilical artery and adverse perinatal outcome (with a sensitivity and specificity of about 60%), it is not clear whether this association is due to the confounding effect of prematurity and abnormal precordial venous flows.[83] Recent series[84] of severely compromised IUGR suggest an independent value of this pattern to predict perinatal morbidity and mortality, with a relative risk of 4.0 and 10.6 for those fetuses with absent or reversed end-diastolic flow, respectively. In addition to increased fetal and neonatal mortality, this finding is also associated with increased risk of long-term abnormal neurodevelopment.[85]

However, a multicenter randomized trial,[86] the growth restriction intervention trial (GRIT), found that early delivery prompted by umbilical artery reversed end-diastolic flow does not improve the mortality rate or the neurological outcome in preterm IUGR fetuses, supporting the concept that a safe interval of 24-48 hours exists to allow for corticoid administration for lung maturation.

Fig. 11: IUGR with paravesical hypogastric—umbilical artery absent diastolic flow

Middle Cerebral Artery

The reduction in the number of functional arterioles in the tertiary villi leads to a decrease in the PO_2 in the fetal blood. This event sets into motion a phenomena of circulatory redistribution principally characterized by the redistribution and centralization of blood flow. The better oxygenated blood goes toward the most vital organs (brain, heart, adrenals), whilst vasoconstriction limits the blood supply at the organs considered less indispensable (digestive system, lungs, skin, skeleton, etc.). As a consequence, a vasodilatation in the cerebral arteries occurs, known as a "brain-sparing" effect. This vasodilatation leads to an increase in the diastolic velocities and a decrease in the resistance and impedance indices in these vessels. The middle cerebral artery has become the standard for the clinical evaluation of the centralization of flow in IUGR fetuses. MCA pulsatility index steadily decrease through gestational age in preterm IUGR fetuses, suggesting a progressive redistribution[87] (Fig. 12).

Moreover, longitudinal studies on deteriorating IUGR fetuses have reported that the pulsatility index in the MCA progressively become abnormal.[87] Up to a 80% of fetuses have vasodilatation 2 weeks before the acute deterioration,[82] although other series have found this figure to be less than

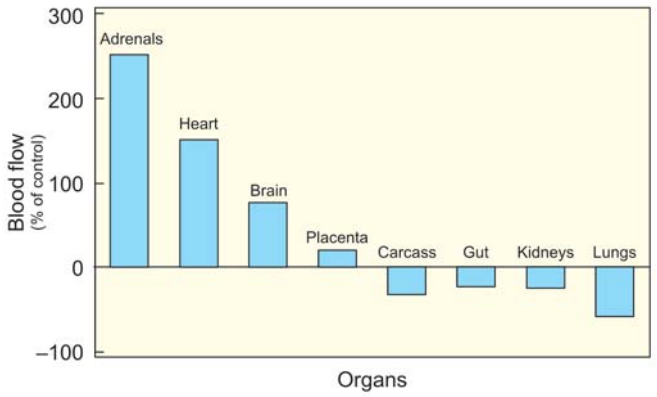

Fig. 12: Redistribution pattern in severe IUGR

50%.[84] Preliminary findings of an acute loss of the MCA vasodilatation in advanced stages of fetal compromise have not been confirmed in more recent series,[82,84,87,88] and, therefore, this sign does not seems to be clinically relevant for management purposes.

The value of cerebral Doppler to predict adverse outcome in the overall population of SGA fetuses is limited, with low sensitivities.[69,75] It has been suggested[89,90] that in near term SGA fetuses, the MCA could be useful to predict adverse outcome, independently of the umbilical artery Doppler. In addition, controversy exists whether cerebral vasodilatation is a merely protective mechanism or on the contrary is associated with suboptimal neurological development.[91] In a longitudinal cohort of infants born preterm (26-33 weeks), accelerated visual maturation was found using visual evoked cortical potentials at 3 years. At 5 years, these series demonstrated that both the changes in cerebral Doppler and the acceleration of visual maturation were associated with a deficit in cognitive scores. Recently, studies in the same cohort confirmed that brain sparing was associated with impaired visual function and visual motor capabilities at 11 years of age.[71,72] In consequence, further evidence is required before recommending its use as an isolated surveillance tool.

Amniotic fluid: It is not well understood the pathways leading to oligohydramnios in fetuses with IUGR. A renal hypoperfusion caused by redistribution phenomena and resulting in a decrease in the urinary production explains only partially this finding. A meta-analysis[92] of 18 randomized studies demonstrated that an amniotic fluid index less than 5 is associated with abnormal 5-minute Apgar score, but failed to demonstrate an association with acidosis.

Longitudinal studies IUGR fetuses have shown that the amniotic fluid index progressively decrease.[84,87] Nowadays, amniotic fluid volume in believed to be a chronic parameter. In fact, among the components of biophysical profile, it is the only one that is not considered acute. One week before the acute deterioration, a 20-30% of cases have oligohydramnios.[84,88]

Acute Markers

Precordial Veins (Ductus Venosus, Inferior Vena Cava and Umbilical Vein)

There is a growing evidence that the fetal heart contributes to the hemodynamic redistribution by shifting the main cardiac output to the left ventricle, maximizing the oxygen supply to the brain. Animal studies have confirmed this adaptative mechanism.[93] Nevertheless, with increasingly adverse condition these cardiac adaptive mechanisms have been suggested to become overburdened, and a progressive impairment of cardiac function has been reported in longitudinal studies[93] (Fig. 13).

Secondary to severe tissue hypoxia, anaerobic metabolism is required for energy production. Chronically, this anaerobic metabolism leads to metabolic academia and acidosis. The fetal myocardium responds to this acidosis with myocardial cell necrosis phenomena, with replacement by fibroid tissue, which affects the myocardial compliance and therefore increase telediastolic pressure at both ventricles. The increased concentrations of troponin-T in neonates with pulsatile umbilical vein[94] suggests that myocardial cell destruction is the underlying cause of precordial veins flow abnormalities, with a decrease in velocities durian atrial contraction and a consequent increase in pulsatility indices.

The association between abnormal precordial veins flows and adverse perinatal outcome has been extensively reported and has been demonstrated to be independent of

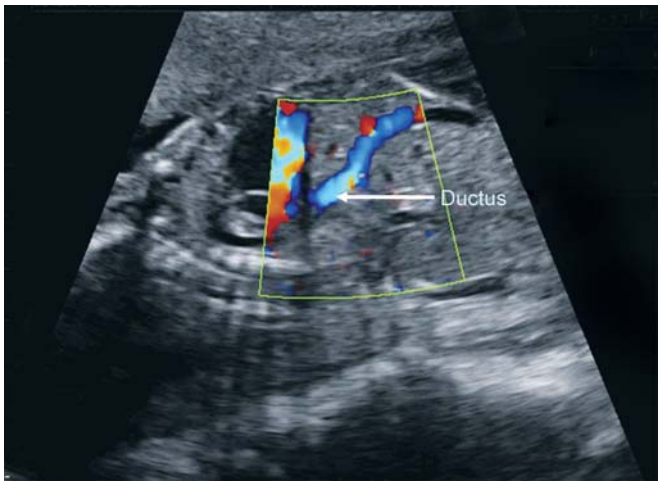

Fig. 13: Ductus venosus color Doppler identification by **aliasing** phenomenon, caused by high velocity and turbulent flow in the ductus

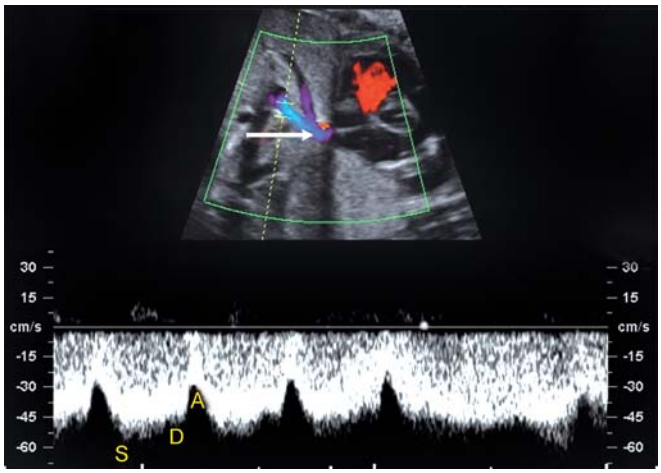

Fig. 14: Ductus venosus spectral Doppler signature

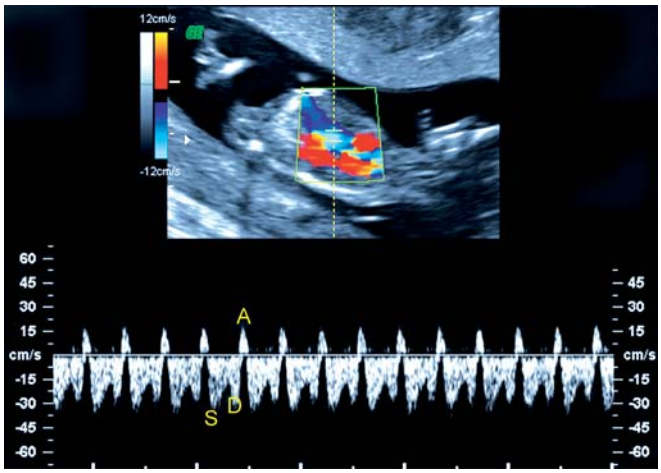

Fig. 15: Reverse a wave in ductus venosus spectral Doppler in a case of trisomia 21

the gestational age at delivery.[83] It has also been shown a correlation with acidosis by cordocentesis[95] (Fig. 14).

The ductus venosus would allow the diversion of highly oxygenated blood from the umbilical vein into the right atria. This preferential blood flow crosses the foramen ovale to the left cavities and hence to irrigate the fetal brain. There are two possible mechanisms for abnormal venous blood flow waveforms in severe hypoxemia. Firstly, the flow redistribution in the umbilical venous blood towards the DV at the expense of hepatic blood flow, and secondly, there may be a myocardial failure. Whereas ductus venous pulsatility index above the 95th centile is an earlier sign, reversed velocities during atrial contraction represents the end of the spectrum of abnormal flow (Fig. 15). It has been reported that in this preterm fetuses, a 3 SD cut-off optimize the combination of sensitivity and specificity.

Moreover, a recent multicentric prospective study demonstrated that ductus venosus Doppler parameters emerge as the primary cardiovascular factor in predicting neonatal outcome in those preterm early-onset IUGR fetuses below 28 weeks. The perinatal mortality when there an absent reversed flow in the a wave was present ranged from 60 to 100%.[97] However, its sensitivity for perinatal death is still 40-70%.

Although each precordial vein correctly predict acid-base status in a significant proportion of IUGR neonates, combination, rather than single vessel assessment provides the best predictive accuracy. Doppler abnormality in either vessel identified about a 90% of newborns with acidosis.[98]

Longitudinal studies have demonstrated that precordial vein flow waveforms become abnormal in advanced stages of fetal compromise.[82,84,87,88] The temporal relation with other acute markers are variable: whereas in about a 50% of cases abnormal ductus venosus precedes the loss of short-term variability in the fetal heart rate, this later sign is the first to become abnormal in the other cases.[87] In about a 90% of cases, the ductus venosus become abnormal only 48-72 hours before the biophysical profile shows changes.[88] Debate exists regarding the advantages of DV Doppler investigation over the biophysical profile. However, observational studies suggest that to integrate both DV Doppler investigation and biophysical profile in the management of pre-term IUGR seems to more effectively stratify IUGR fetuses into risk categories. Further research is warranted to investigate how they are best combined.

Other Cardiac Doppler Parameters

The aortic isthmus is a link between the right and left ventricles which perfuse the lower body and placental circulation, and upper body, respectively. Consequently, its blood flow pattern reflects the balance between both ventricular outputs and the existence of differences in the vascular impedance in either vascular system. The clinical use of aortic isthmus waveforms for monitoring fetal deterioration in IUGR has been limited, but preliminary work suggests that abnormal AOI impedance indices are an intermediate step between placental insufficiency-hypoxemia and cardiac decompensation.[99] A prospective study in severe early-onset IUGR demonstrated that a retrograde flow in the AOI in growth-restricted fetuses correlated strongly with adverse perinatal outcome.[100]

Hypoxemia and acidosis may also impair cardiac contractility directly. The myocardial performance index (MPI) is a novel method in fetal medicine that assesses both systolic and diastolic functions by including the measurement of isovolumetric and ejection times and would be

useful in assessing the progressive hemodynamic deterioration. It has been recently reported to be independently associated with perinatal mortality, mainly in very pre-term IUGR fetuses,[101] although its role as a surveillance tool needs to be further elucidated.

Fetal Heart Rate

Due to severe hypoxemia, signal from peripheral chemo and baroreceptors triggers a parasympathic response that results in fetal heart decelerations. In advanced stages of fetal compromise, the direct effect of acidosis on the nervous system and on the myocardium result in a loss of the fetal heart rate variability as well as deceleration.

Early studies on high-risk demonstrated that though highly sensitive, a 50% rate of false positive hampers, it clinical usefulness. In addition, a meta-analysis[102] on high-risk pregnancies failed to demonstrated any beneficial effect in reducing perinatal mortality. Hence, there is no evidence to support the use of traditional fetal heart-rate in IUGR fetuses.

Computerized fetal heart-rate analyses has provided new insight into the pathophysiology of IUGR. It has been demonstrated by cordocentesis that the short-term variability closely correlates with acidosis and severe hypoxia. Despite the fact that Bracero et al[103] demonstrated non-significant perinatal outcome differences between visual and computerized FHR, more recent longitudinal series pointed out a potential role as acute marker.[87] Short-term variability become abnormal coinciding with the ductus venosus: whereas in about a 50% of cases abnormal ductus venosus precedes the loss of short-term variability in the fetal heart rate, this later sign is the first to become abnormal in the other cases.[87] Both parameters are considered acute responses to fetal acidosis.

The sequence of the pathophysiological mechanisms and biophysical signals can be observed in Figure 16.

Biophysical Profile

Among the components of the Manning[104] biophysical profile, amniotic fluid volume is the more chronic parameter. With increasing fetal compromise, the amniotic fluid volume progressively decreases.[84,87] In advances stages of hypoxia, a decrease in the breathing movements is observed, and finally, mainly acidosis accounts for the loss of fetal tone and gross body movements.

Observational studies demonstrated an association between abnormal biophysical profile and perinatal mortality and cerebral palsy.[105] Studies in which a cordocentesis was performed demonstrated a good correlation with acidosis,[106] being the fetal tone and gross motor movements the best correlated components. However, similarly to the fetal heart rate, although highly sensitive, a 50% rate of false positive limits the clinical usefulness of the biophysical profile.[107] A meta-analysis[108] showed no significant benefit of biophysical profile in high-risk pregnancies, but more recent series[109] on IUGR have suggested that Doppler both Doppler and BPS effectively stratify IUGR fetuses into risk categories. Since fetal deterioration appears to be independently reflected by both tests further studies are warranted to proof the usefulness of combined both testing modalities. The above mentioned study uses a cut-off of 4 (or 6 if oligohydramnios exists), for the time being these are the more comprehensive criteria for decision-making.

Longitudinal series[88] have demonstrated that except for the amniotic fluid volume and the fetal heart-rate, the other components of the biophysical profile become abnormal in advanced stages of fetal compromise: In about a 90% of cases, the ductus venosus become abnormal only 48-72 hours before the biophysical profile.[88]

OBSTETRIC MANAGEMENT

Despite clear guidelines supported by strong evidence can not be provided, protocols for management of SGA fetus may be developed according to current knowledge. It is evident that an integrated approach seems most appropriate when using any Doppler algorithm in management. Our protocol is as follows:

1. Normal-SGA (estimated fetal weight below the 10th centile with normal cerebroplacental ratio and normal uterine artery Doppler flow): excluding infectious and genetic causes, the perinatal results are good. Fortnightly Doppler and biophysical profile are performed. Delivery should only be indicated for obstetrics or maternal factors. A vaginal delivery with continuous fetal monitoring is recommended. Delivery should not be postponed more than 40 weeks of gestation.
2. IUGR with normal fetal well-being tests (estimated fetal weight below the 10th centile with abnormal cerebroplacental ratio but no presence of vasodilation or uterine artery Doppler flow): weekly Doppler and biophysical profile are performed. Delivery beyond 37 weeks or when pulmonary maturity is proven, could be considered. A vaginal delivery with continuous fetal monitoring is recommended.

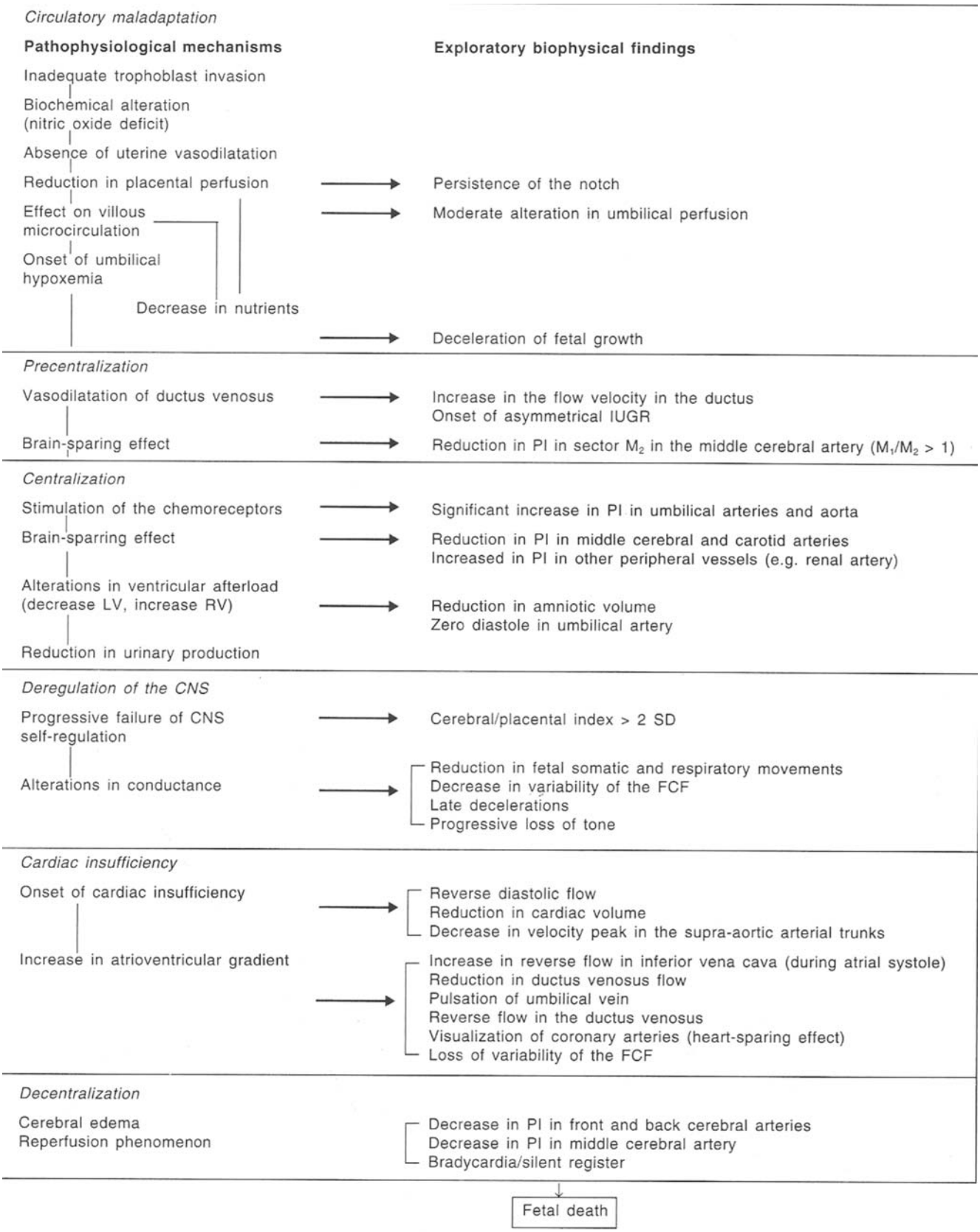

Fig. 16: Sequence of the pathophysiological mechanisms and biophysical signals. IUGR: Intrauterine growth restriction; PI: pulsatility index; LV: Left ventricle; RV: Right ventricle; CNS: Central nervous system; FCF: Fetal cardiac frequency

3. IUGR (estimated fetal weight below the 10th centile with abnormal cerebroplacental ratio or uterine artery Doppler flow) with significant placental insufficiency (absent end-diastolic flow in the umbilical artery) or centralization (persistent vasodilatation of middle cerebral artery):
   a. Beyond 34 weeks: A vaginal delivery is accepted. A cesarean section would be required in absent end-diastolic umbilical flow.
   b. Between 32 and 34 weeks:
      i. Reversed end-diastolic flow: steroids and deliver in 24-48 hours by cesarean section.
      ii. Absent end-diatolic flow: steroids, daily Doppler and biophysical profile until 34 weeks.
   c. Below 32 weeks: steroids, daily Doppler and biophysical profile until 34 weeks.
4. IUGR (estimated fetal weight below the 10th centile with abnormal cerebroplacental ratio or uterine artery Doppler flow) with suspected fetal compromise (persistent increased ductus venosus waveforms pulsatility, low short-term variability, abnormal biophysical profile):
   a. Beyond 32 weeks: deliver by cesarean section.
   b. Below 32 weeks: hospital admission, steroids, daily Doppler and biophysical profile/12 hours until 32 weeks.
5. IUGR (estimated fetal weight below the 10th centile with abnormal cerebroplacental ratio or uterine artery Doppler flow) with fetal decompensation (persistent absent or reversed a-wave in the ductus venosus or persistent pulsatile umbilical vein or persistent abnormal biophysical profile or decelerative cardiotocography): deliver by cesarean section at a tertiary care center. In the subgroup under 28 weeks, each case should be evaluated by a multidisciplinary committee composed by an obstetrician and a neonatologist with experience in those case, and taking into account the opinion of the parents: expectant management could be an option is this extremely preterm and compromised fetuses.

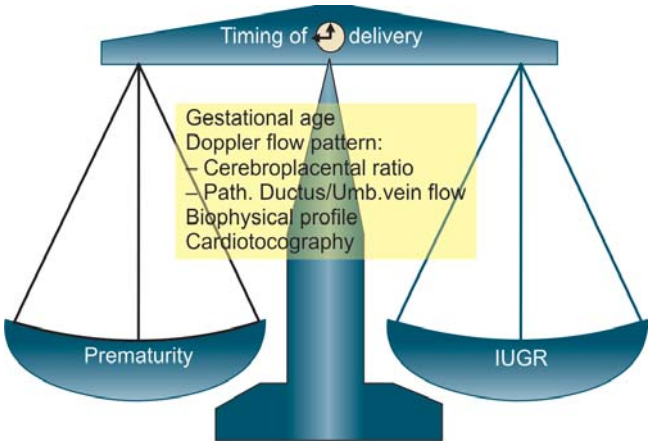

Fig. 17: Obstetric management of IUGR

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