Review

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The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature.

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Abstract

Intrauterine growth restriction (IUGR) represents a serious condition that can lead to increased perinatal morbidity, mortality and postnatal impaired neurodevelopment. There are two distinct phenotypes of IUGR: early onset and late onset IUGR with different onset, patterns of evolution and fetal Doppler profile. In early onset preeclampsia the main Doppler modifications are at the level of umbilical artery, with progressive augmentation of the pulsatility index to absent or reverse end diastolic flow. The modifications of the cerebral, cardiac and ductus venosus circulation are generally present, but with different sequences. The late onset IUGR is determined by third trimester placental insufficiency that entails fetal hypoxia. The cerebro-placental ratio (CPR) and the pulsatility index of the middle cerebral artery (PI MCA) seems to be the main markers for both diagnosis and obstetrical management while umbilical Doppler PI is frequently normal. Also the sequence of Doppler alterations is neither specific nor complete. New protocols for the diagnosis and management of late onset IUGR need to be implemented.

Keywords: IUGR, Doppler, umbilical artery, middle cerebral artery

Introduction

The Doppler examination represents nowadays an important tool in the evaluation of normal and pathologic pregnancies allowing appropriate characterization of the fetal status, detection and extension of fetal distress, investigation of the fetal protective mechanisms or decompensation.

Fetal growth is the results of the maternal availability of nutrients, placental transfer, and fetal own growth potential [1]. Neonates with a birth weight under the 10th percentile were considered small-for-gestational-age (SGA) [2]. In order to exclude healthy small babies, severe intra-uterine growth retardation (IUGR) includes all fetuses with an estimated fetal weight under 5th or even 3rd percentile [3,4], known to be associated with an increased mortality or morbidity. The latest data from the USA reveals in 2013 an increase with 10% of low birth rate between 1990 and 2006 in singletons [2]. The problem of low birth weight fetuses remains very current, the absolute fetal weight being considered an independent prognostic factor for fetal mortality [3].

Doppler examination is based on the hemodynamic of blood circulation, involving speed, turbulences, vascular reactivity, resistance, and vascular bed geometry. All these characteristics allow the evaluation of the fetal hemodynamic response to stress [5]. The Doppler assessment is extremely useful for the evaluation of the fetal arterial circulation, of the cardiac function and of the venous system permitting a better characterization of the fetal status [1]. Normal aspect of MCA (middle cerebral artery) is presented in figure 1.

Doppler ultrasound together with the biophysical profile, amniotic fluid index, and cardiotocography plays a very important role in the follow-up algorithm of the IUGR fetuses [6-8].

There is an emerging number of recent studies that confirms that cerebral vascular modifications in late-onset IUGR or even appropriate from gestational age

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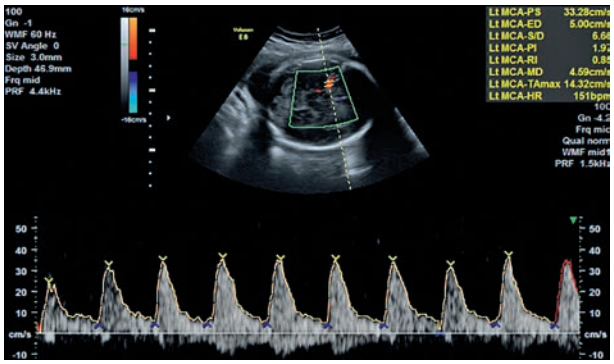


Fig 1. Normal aspect of middle cerebral artery circulation, with low diastole.

(AGA) fetuses are associated with adverse perinatal outcome and potential long term neurological sequels [9]. Early detection could potentially modify the obstetrical management and determine an optimized outcome.

Physiopathology of IUGR

Placentation is the determinant factor for developing early (E-IUGR) or late (L-IUGR) IUGR [10]. Doppler examination analyses the circulatory modifications of the fetus that can be either lesional or adaptive reactions. Classically, it was supposed that fetuses at any age of gestation had the same pattern of reactions in face of a progressive hypoxia. Recent studies in humans and in lamb models suggest that in fact, the fetus reacts differently at a specific age of gestation [11]. The two phenotypes of IUGR (earl and late) are distinct by the moment of onset, evolution, Doppler parameters modifications, and postnatal outcome [9]. The best cut-off between the two IUGR forms is 32 weeks in terms of perinatal outcome [10].

The cerebro-placental ratio (CPR) represents the ratio between the MCA pulsatility index (MCA PI) and the umbilical artery pulsatility index (UA PI); in normal fetuses is supposed to be superior to one [12]. It is an extremely useful tool in the assessment of vascular cerebral hemodynamics in pregnancies complicated with IUGR where it realizes the quantification of the brain-sparring effect [12].

Growth-restricted fetuses have an augmented risk of mortality and morbidity [13,14]. The severe morbidity is represented by intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, infections, pulmonary hemorrhage, hypothermia and hypoglycemia [14]. The antenatal diagnosis, treatment and timely delivery could diminish the risks significantly [15].

E-IUGR

The E-IUGR is determined by massive lesions or dysfunctions of the placental structure, taking place during first and second trimesters of pregnancy due to inappropriate trophoblastic invasion of spiral arteries. Therefore E-IUGR it is considered to be a vascular disorder due to the abnormalities of the tertiary villous vessels [16,17].

It is more frequently encountered in patients with preeclampsia, autoimmune disorders or other conditions that can affect the placental vessels [18]. E-IUGR is more frequently linked to early onset preeclampsia, while L-IUGR is not as connected to preeclampsia [19]. If IUGR is detected earlier in pregnancy the likelihood to progress is higher [16].

The alteration of placentation has an important impact upon fetal growth, the most affected being the abdominal circumference while the biparietal diameter and the femur length are less modified [20,21]. In this type of IUGR the evolution is long enough to permit the development of a classic fetal asymmetrical hypotrophy that can be diagnosed by fetal ultrasound [22]. This long evolution is mainly due to the small oxygen demands of the fetal brain and to the long resistance of the fetal heart at this age of gestation [11,22].

From the maternal point of view, Doppler examination of the uterine arteries in the first and second trimester can confirm the presence of a vascular pathology and can anticipate its evolution [23]. The sensitivity of uterine Doppler examination in the first trimester upon any IUGR detection is 15.4% (95% CI: 12.4-18.9) with a high specificity 93.3% (95% CI: 90.9-95.1) [23]. The performance upon E-IUGR is better – sensibility - 39.2% (95% CI: 26.3-53.8) and respectively specificity 93.1% (95% CI: 90.6-95.0) [23].

The sequence of classical Doppler alteration is usually respected in E-IUGR [16]. Therefore the deterioration of fetal Doppler parameters is progressive; first the umbilical artery indexes being modified and only secondarily the cerebral Doppler aspect [16]. Until the terminal lesions of the fetal brain and the cardiotocographic signs of severe distress, there is time for all the successive and sequential Doppler vascular modifications to develop: peripheral vasoconstriction with augmented umbilical artery pulsatility index (UA PI), cerebral vasodilatation (fig 2) with a reduction of the middle cerebral artery pulsatility index (MCA PI), absent end-diastolic/ reverse flow in umbilical artery (AREDF – fig 3), absent “a” wave in ductus venosus, cardiac diastolic and systolic insufficiency and overload of the precordial venous system with “a” wave negative on ductus venosus [22]. Also the rapidity of progression of Doppler anomalies (UA, MCA,

and DV) seems to be faster in E-IUGR [9,16]. Even if this classic sequential deterioration of Doppler indices is the most frequent in E-IUGR, others sequences are also possible as Unterscheider et al demonstrated in 2013 in the PORTO study [4].

Also, in E-IUGR the absent end-diastolic flow or reverse flow in umbilical artery are better correlated with the fetal outcome than the CPR [24]. Absent or reversed UA end diastolic velocity has an independent impact on neurodevelopment after 24-26 weeks [24]. These children have a lower motor developmental index at age 2 and lower cognitive performance [25]. The MCA PI less than 5 centile is also an efficient tool for the evaluation of the cerebral vasodilatation. A recent study from 2014 on 881 fetuses with E- IUGR, analyzing the aggregate morbidity and the mortality of IUGR fetuses found that CPR<1 regardless of the evaluation methods, is associated with a poor perinatal outcome (OR=11.7, p<0.001); moreover all three fetal deaths were associated with a CPR<1 [26]. Another finding of the above mentioned study is that MCA can be evaluated using IR or IP, the results being similar [26].

The abnormal cerebroplacental ratio was found to be superior to biophysical profile in fetuses with E-IUGR

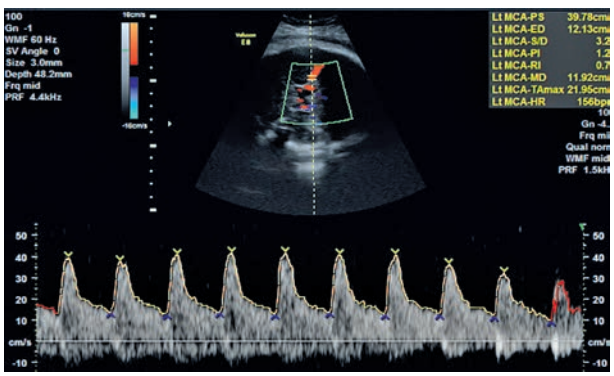


Fig 2. Cerebral vasodilatation in middle cerebral artery with increased diastole.

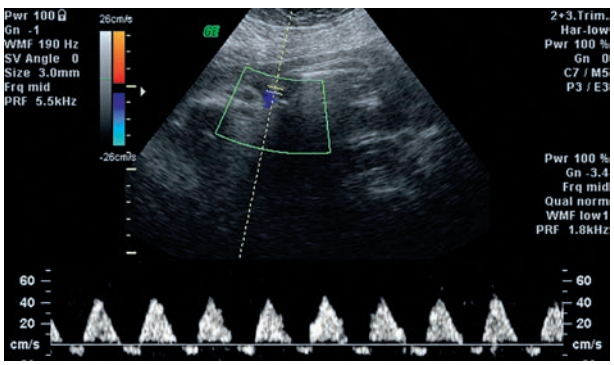


Fig 3. Reverse flow in umbilical artery.

for the prediction of adverse pregnancy outcome [27,28] such as higher rates of prematurity, low birth weight, high rate of caesarean section, Apgar score inferior to 7 at 5 minutes, increased rate of fetal acidosis, adverse neonatal outcome, neonatal intensive care unit admission and perinatal death [26,27,29]. Moreover it has been shown that in E-IUGR the CPR is highly correlated with ante and postpartum outcome [27] but there are others studies that demonstrate the superior role of umbilical indices in these cases. In 2010 van der Broek et al showed that UA Doppler results, gestational age at delivery and the degree of growth restriction are the best predictor of the neurodevelopmental evolution during childhood, and that venous, cerebral or cardiac Doppler studies, do not add an independent risk stratification [24]. Also, Baschat et al in 2014 concluded that gestational age, umbilical and cerebral Doppler, and the circumstances surrounding delivery are the most powerful predictor of clinical deterioration [9].

L-IUGR

L-IUGR represents the failure of the fetus to reach growth potential at term. Fetal hypoxemia/hypoxia secondary of placental insufficiency represents the main cause of L-IUGR. In most of the cases the placental lesions do not have a significant extent in order to increase the resistivity of the placenta and translated into augmented UA IP [9]. In terms of frequency, L-IUGR is far more prevalent than E-IUGR [30]. It is associated with the pathological specimen with multiple placental anomalies such as villous immaturity that have less impact upon placental resistance; therefore, the umbilical Doppler indices are unaffected [9].

The diagnosis of L- IUGR is more difficult, due to the large variability of fetal parameters on growth charts in the third trimester [4,31]. L-IUGR can be suspected when the individual growth curve slows down or even become flat [32] (fig 4). Another situation when the presence of L-IUGR can be assumed is when an increase of the head circumference/abdomen circumference ratio (HC/AC) is detected in previous "normal" growing fetus [32].

The fetal brain at term has increased requirements of oxygen; therefore the first hemodynamic alteration in the presence of hypoxia is the cerebral vasodilatation. Even if vasodilatation itself is a method of neuro-protection, it cannot completely compensate the effects of hypoxia [33]. In these particular cases the cardiac insufficiency does not have enough time to arise; the severity of the cerebral lesions taking place faster determine severe CTG alterations. In these cases the classical sequence of Doppler modifications is not present [4,9].

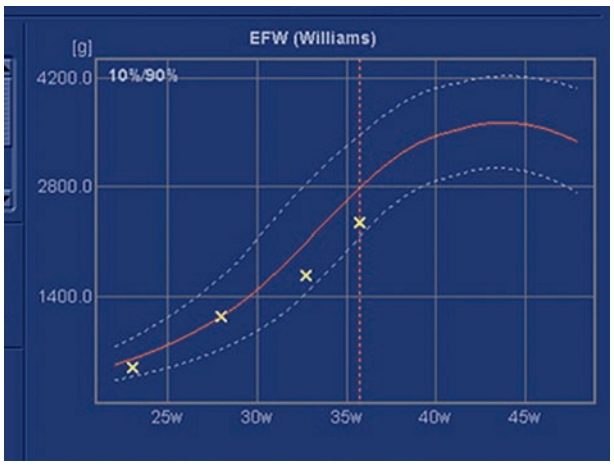


Fig 4. Ultrasound diagnosis of late IUGR. Slowing down of the fetal weight evolution.

L-IUGR fetuses are very fragile, despite the fact that they are not as affected by prematurity compared to E-IUGR, due to increased oxygen requirements of their brain [34]. Consequently they bare multiple risks mainly due to their inability to tolerate hypoxia. The reactive cerebral redistribution in L-IUGR fetuses is associated with an alteration of the brain metabolism [34].

Undetected IUGR in the third trimester of pregnancy represents the main cause of unexplained stillbirths in low-risk pregnancies. IUGR was identified in 43% respectively in 52% of unexplained stillbirths'; hence, IUGR represents the strongest risk factor for an unexplained intrauterine death [35,36]. Moreover, probably a number of idiopathic cases of cerebral neonatal palsy where an acute intrapartum hypoxic event could not be identified, are in fact caused by an undetected L-IUGR.

The phenotype of L- IUGR and the role of the Doppler examination are relative new issues but there are a significant emerging number of studies that sustain the existence of this condition and the usefulness of cerebral Doppler examination in this period of pregnancy [9]. Studies on this topic dates back to 2000 when first reports came out showing cases of L- IUGR with normal UA Doppler findings associated with poor obstetrical outcome [32]. The UA Doppler failed to identify fetal compromise in a significant number of late SGA fetuses [32]. Additionally, in fetuses with L- IUGR the placental insufficiency seems not to be reflected in UA Doppler [37].

Moreover, recently (2013), the PORTO study evaluated the vascular modifications and their sequence in multiple fetal vessels and myocardial performance index on a set of 1116 IUGR pregnancies [4]. The sequences of alteration were analyzed related to the perinatal outcome [4]. The main conclusion was that multiple possible patterns of Doppler sequence alteration exist in IUGR fetuses and that the classic sequence of deterioration, in which the UA Doppler is the first modified finding, is present in only 46% of cases; hence UA Doppler cannot be used alone for the surveillance and moment of delivery in IUGR pregnancies [4].

L-IUGR is a challenging diagnosis unfortunately associated with increased fetal morbidity and mortality, impaired postnatal outcome and with suboptimal neurodevelopment [9]. UA Doppler and the sequence of Doppler modifications in multiple fetal vessels are not reliable for the fetal surveillance [4,37]. Recent papers focus on Doppler markers of cerebral vasodilatation that seems to be a landmark of L-IUGR. The parameters that have been frequently assessed were the PI of the MCA and the cerebro-placental ratio (CPR) [27,32,37-39].

Another method used for the evaluation of fetal cerebral vasodilatation is MCA PI. Thus an MCA PI < 5% is considered a marker of cerebral vasodilatation even in the presence of a normal UA PI. MCA PI trend is more important that its intrinsic value; even if the indexes remain in the normal range, the evolution in a pathologic direction may be an indicator of fetal hypoxia [40]. The study of Ebbing et al gives the longitudinal reference ranges [41].

CPR may be modified before the MCA IP becomes abnormal, being a more precocious and sensible tool for the diagnosis of cerebral vasodilatation. A value of CPR < 1 mg/dl is used for the diagnosis of cerebral vasodilatation [27]. The CPR can be more precisely assessed by calculating the MoM (multiple of median) for a specific age. A value of CPR superior to 0.675 MoM is considered to be associated with significant cerebral vasodilatation [42]. Online software is available for CPR MoM calculations [43].

Doppler evaluation of the MCA is crucial for L-IUGR fetuses after 35 gestational weeks having a good correlation with fetal morbidity and mortality [32]. Cerebral redistribution was also correlated with a higher rate of cesarean section. [32]. Moreover, in fetuses with L-IUGR, abnormal CRP was associated with a significant increased rate of fetal distress in labor, lower umbilical cord pH and higher rate of admittance to neonatal intensive care unit [38]. Therefore, in L-IUGR fetuses, CRP is a better predictor than MCA modifications alone [38,39]. Moreover, the Doppler indices of UAs were mainly normal. Thus, the Doppler evaluation of the MCA in mandatory and the CPR must be calculated. If in the third trimester, the obstetrician analyses only the UA PI, these fetuses will be missed and the potential intrapartum and postnatal complications cannot be anticipated [39].

An abnormal CPR and low birthweight centile were identified as significantly and independently associated with emergency caesarean section in both appropriate for gestational age (AGA) and L-IUGR groups [44]. CPR performed better in identifying fetuses with adverse outcome than the biophysical profile did [28]. Moreover, CPR was a better predictor for the birthweight centile regarding the necessity of admission to the neonatal intensive care unit [44]. These data encourage the recommendation of usage of CPR for risk stratification in L-IUGR fetuses [27].

The short and medium neonatal outcome seems to be also influenced by the cerebral vasodilatation. Meher et al found that at term, SGAs fetuses cerebral redistribution was associated with an increased risk of neonatal motor activity, lower score of communication and problem solving scores at 2 years of age [33]. Term IUGR fetuses have poorer neurodevelopmental outcomes compared with those with normal growth. This may suggest the development of a neurological injury from early stages of fetal hemodynamic adaptation to hypoxia [45].

The rates of acute fetal distress during delivery and the number of emergency caesarean sections in L-IUGR with cerebral redistribution are significantly increased [27,33,44].

Implications for clinical practice

The use of Doppler evaluation of the uterine arteries during the first and second trimester of pregnancy represents a helpful tool for the prediction of IUGR [2,23,46,47].

Once an early/late IUGR fetus has been identified based on the ultrasound measurements, the evaluation must include the Doppler analysis of umbilical and cerebral circulation (CPR, MCA) [27]. This evaluation allows the risk stratification of IUGR fetuses pointing out the fetuses with an increased risk for perinatal complications.

UA Doppler is used for the surveillance and obstetrical management of fetuses with E-IUGR. The timing of delivery should be chosen taking into account the gestational age, umbilical Doppler, MCA Doppler, ductus venosus Doppler, cardiotocography, and biophysical profile [6-8].

In fetuses with L-IUGR, frequently the UA Doppler reading is within normal range, therefore it cannot constitute a useful diagnosis. The cerebral vasodilatation being the first reaction of the fetus to hypoxia in L-IUGR, the MCA Doppler is usually modified, therefore becoming the most valuable examination tool for this condition. No specific sequence of Doppler alteration can be identified, therefore any scenario is possible [4]. In this period the fetal cerebral resistance to hypoxia is inferior to the cardiac one, so it is possible to have major fetal accidents before cardiac and ductus venosus Doppler modification appears. There are cases with severe fetal distress, with pathologic CTG but without venous modifications.

The CPR should be considered as an assessment tool in fetuses undergoing third-trimester ultrasound examination, regardless of the results of the umbilical artery and middle cerebral artery measurements [27]. Early diagnosis of fetal hypoxia in the third trimester can optimize the obstetrical management and thus, the neonatal outcome.

Even in AGA fetuses during the third trimester, those with a modified CPR are at an increased risk of perinatal complications. There are discussions about the utility of routine 3rd trimester ultrasound for all pregnancies [27,48]. Due to the good correlation of CRP in AGA and IUGR with the acidemia at birth, neonatal morbidity and neurologic outcome, the CRP evaluation at term or at the time of admission at the delivery room can be proposed as a screening test. This approach needs further studies [27,44,48].

The MCA Doppler evaluation is important for the decision of the delivery timing especially when the UA Doppler is normal. Recent guidelines recommend delivery of L-IUGR fetuses with brain sparring effect, because it is predictive of acidosis at birth [7]. There is also growing evidence that cerebral redistribution may be used in association with other clinical elements in the decision of delivery of L-IUGR fetuses, even in the presence of a normal UA Doppler. After 34 weeks, the risk of serious morbidity and of mortality is low and the delivery of the fetuses with L-IUGR will minimize the long term sequelae [33].

In conclusion, the diagnosis of fetal hypoxia in the third trimester remains a challenge for modern obstetrics. The paradigm that a normal UA Doppler pattern in the third trimester confirms a normal pregnancy and does not need any further Doppler evaluation of other fetal vessels definitely requires modification [30] and has an important impact on the clinical follow-up.

Conflict of interest: none

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