Cerebral and cardiac doppler parameters in the identification of fetuses with late-onset intrauterine growth restriction at risk of adverse perinatal and neurobehavioral outcome

Rogelio Cruz Martínez

UNIVERSITAT DE BARCELONA

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CEREBRAL AND CARDIAC DOPPLER PARAMETERS IN THE IDENTIFICATION OF FETUSES WITH LATE-ONSET INTRAUTERINE GROWTH RESTRICTION AT RISK OF ADVERSE PERINATAL AND NEUROBEHAVIORAL OUTCOME

Submitted by

Rogelio Cruz Martínez

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Director:

Professor Eduard Gratacós Solsona
Department of Maternal-Fetal Medicine
Hospital Clínic, University of Barcelona, Spain

Codirector:

Professor Francesc Figueras Retuerta
Department of Maternal-Fetal Medicine
Hospital Clínic, University of Barcelona, Spain

Professor Eduard Gratacós Solsona

Department of Maternal-Fetal Medicine
Hospital Clínic, University of Barcelona, Spain

Professor Francesc Figueras Retuerta

Department of Maternal-Fetal Medicine
Hospital Clínic, University of Barcelona, Spain

We confirm that Rogelio Cruz Martínez has realized under our supervision the studies presented in the thesis **"Cerebral and cardiac Doppler parameters in the identification of fetuses with late-onset intrauterine growth restriction at risk of adverse perinatal and neurobehavioral outcome".**

The present thesis has been structured following the normative for PhD thesis as a compendium of publications for the degree of Doctor of European Doctor in medicine, and that the mentioned studies are ready to be presented to the Tribunal.

Eduard Gratacós Solsona **Francesc Figueras Retuerta**

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1. INTRODUCTION

1.1 Intrauterine Growth Restriction vs. Small for Gestational Age

A fetus is considered growth-restricted when sonographically measured fetal dimensions, particularly fetal weight estimated from multiple biometric measurements below 10th centile (Ott, 2006, Hadlock et al., 1985, Maulik, 2006). However; this approach can not differentiate constitutional fetal smallness from fetal growth failure. Because fetal growth restriction is a late manifestation of early abnormal placental development, when is confirmed, is necessary to differentiate SGA and IUGR, to identify fetuses who are small due to placental dysfunction and who required early intervention assessing placental function with Doppler ultrasound (Maulik, 2006, Kinzler and Vintzileos, 2008, Tan and Yeo, 2005). SGA fetuses are those identified by a fetal estimated weight below10th centile and a negative screen for abnormal placental or fetal Doppler, or evidence of genetic syndrome or fetal infections. When fetal estimated weight is low together with abnormal placental and fetal Doppler are considered true IUGR due to placental insufficiency(Cruz-Martinez and Figueras, 2009).

Recently, with improved ultrasound imaging and the advent of Doppler studies, it has become obvious that, within the descriptive term SGA, there are separate groups with distinct etiologies and prognoses. Therefore, it is generally accepted that normal SGA and IUGR must be considered separately (Soothill et al., 1999). Population birthweight centiles, which account for fetal sex and gestational age at delivery, are typically used to classify size at birth. Unfortunately, due to the wide biologic variability in human size, interplay a number of genetic and physiological factors, such as sex, maternal body mass index, and ethnic group; is necessary to construct normal curves for each population, utilizing a birth weight centile cutoff to identify fetuses at significant risk of compromise more adequately (Groom et al., 2007, McCowan et al., 2005, Figueras et al., 2007, Figueras et al., 2008c). For our population, Figueras *et al.*(Figueras et al., 2008c) classified no anomalous singleton pregnancies deliveries after 24 weeks gestation as SGA (<10th centile) or appropriate to gestational age (AGA) based on either a population-based standard.

1.2 Early vs. late-onset intrauterine growth restriction

Fetal growth restriction is associated with a high risk of perinatal morbidity and mortality, and has been described as responsible for 50% and 20% of preterm and term perinatal deaths, respectively (S and Gardosi, 2004). Since not all fetuses found to be small in utero have true growth restriction, the distinction of placental insufficiency from constitutional smallness has been one of the goals of fetal medicine over the last 20 years. The most widely used sign to identify placental insufficiency, and consequently to diagnose IUGR, is an elevated pulsatility index (PI) in the umbilical artery (UA) (Lackman et al., 2001a, Lackman et al., 2001b).

Fetuses with early-onset intrauterine growth restriction (IUGR) resulting from severe placental insufficiency are at increased risk for adverse short and long term outcomes (Bernstein et al., 2000). There is also evidence to suggest an association between IUGR and poor neurological outcome, cognitive deficit, attention capacity and behavior problems (Yanney and Marlow, 2004, Walker and Marlow, 2008). IUGR children are also associated with poor academic performance, low social competence, behavioural problems (Doctor et al., 2001, Lundgren et al., 2001) and cerebral palsy (Spinillo et al., 2006, Jarvis et al., 2006, Blair and Stanley, 1990).

Small fetuses with normal UA Doppler are normally defined as small-for-gestational-age (SGA), and earlier reports suggested that they might essentially represent constitutionally small fetuses (Soothill et al., 1999). However, recent evidence suggests that this diagnostic category contains a proportion of cases with true forms of fetal growth restriction where the degree of placental insufficiency is not reflected in the UA Doppler. Clinical studies have reported an increased risk of adverse perinatal outcome(McCowan et al., 2000b, Doctor et al., 2001, Figueras et al., 2008a), and emergency intrapartum cesarean section for fetal distress in these fetuses.(Severi et al., 2002) In addition, we and other groups have recently published that a considerable proportion of these fetuses show abnormal neurobehaviour neonatally (Padidela and Bhat, 2003, McCowan et al., 2002, Als et al., 1976) and suboptimal neurodevelopmental tests in childhood (Figueras et al., 2008b).

Aside for the neurodevelopmental outcome, previous studies have demonstrated that SGA fetuses with normal UA Doppler are associated with subclinical biochemical and ecochardiogaphic signs of cardiac dysfunction in the neonatal period (Chaiworapongsa et al., 2002, Girsen et al., 2007a, Girsen et al., 2007b) and in childhood(Crispi et al., 2010). In keeping with this contention, Girsen et al(Girsen et al., 2007a, Girsen et al., 2007b) reported that 30-40% of the SGA fetuses with normal UA Doppler have increased secretion of fetal erythropoietin and N-terminal peptide of proB-type natriuretic peptide. Similarly, Crispi et al. (Crispi et al., 2010) published that these fetuses have cardiac remodeling and echocardiographic subclinical signs of cardiac dysfunction in childhood as compared with normally grown children born at the same gestational age.

Since the identification of SGA fetuses with true growth restriction cannot be based on UA Doppler, and hence recent research has focused in the investigation of further parameters which may allow identification of cases with IUGR in order to plan timely delivery and early interventions to prevent long-term consequences(Froen et al., 2004).

1.3 Middle cerebral artery

Chronic hypoxia is associated with a redistribution of blood flow, presumably through their action on chemo- and baroreceptors. This mechanism allows preferential delivery of nutrients and oxygen to vital organs like the brain. As a consequence, a vasodilatation in the cerebral arteries occurs, known as a brain-sparing effect (Scherjon et al., 1993). In clinical practice, brain sparing is identified by a middle cerebral artery (MCA) Doppler PI below the 5th percentile(Dubiel et al., 2002). Recent studies have demonstrated that 15-20% of term SGA fetuses with normal UA Doppler have reduced PI in the MCA, and that this sign is associated with poorer perinatal outcome (Hershkovitz et al., 2000, Severi et al., 2002). In addition, SGA fetuses with MCA vasodilation have an increased risk of abnormal neurobehaviour neonatally (Oros et al., 2007) and at two years of age (Eixarch et al., 2008). These studies support the use of brain Doppler evaluation to distinguish SGA with growth restriction from constitutional smallness. However, vasodilatation of the MCA might have a poor sensitivity to detect fetuses in the initial stages of increased brain perfusion and therefore, additional parameters to early detect brain redistribution changes are required.

1.4 Cerebroplacental ratio

The cerebroplacental ratio (CPR) is calculated by simple division of the MCA by the UA pulsatility indices. Consequently, CPR may be decreased even when UA and MCA values are very close to normal(Gramellini et al., 1992). The CPR offers the advantage of detecting the redistribution of blood flow due to two potential mechanisms. Firstly, the centralization that may be observed with elevated placental blood flow resistance, and secondly, the decreasing cerebral blood flow resistance due to “brain sparing”. The combination of MCA and UA Doppler in the CPR improves further the prediction of adverse perinatal outcome in preterm IUGR(Gramellini et al., 1992, Jain et al., 2004, Odibo et al., 2005, Habek et al., 2007). In addition, longitudinal Doppler studies in term SGA fetuses suggest that MCA PI is reduced in a later stage than other brain vessels, such as the CPR(Oros et al., 2010) which open the possibility to introduce this parameter to improve the identification of late-onset IUGR fetuses.

1.5 Cerebral blood perfusion

Hemodynamic evaluation by conventional spectral Doppler does not directly reflect changes in tissue perfusion because it has a low sensitivity in measuring subtle changes in blood movement within the small vessels (Fortunato, 1996, Gudmundsson et al., 1998, Rubin et al., 1994). In an attempt to increase the sensitivity of the spectral Doppler evaluation, cerebral blood perfusion has been estimated using power Doppler ultrasound. Fractional Moving Blood Volume (FMBV) is a new method proposed by Rubin *et al*. (Rubin et al., 1995) to quantify blood perfusion using power Doppler ultrasound (Welsh, 2004). FMBV indentify signals coming from “true blood” and excluding those from artifacts or tissue movements by a double normalization process (Rubin et al., 1997, Welsh, 2004, Welsh et al., 2005, Rubin et al., 1995). This technique has shown an excellent correlation with gold standards in the estimation of true tissue blood flow in animal experiments (Hernandez-Andrade et al., 2004). Thus, the method has shown a good reproducibility in the assessment of brain perfusion in human fetuses in the three studied regions included in this study, with an inter-observer variability <10% and a high intra-observer agreement (intraclass correlation coefficient above 0.9)(Hernandez-Andrade et al., 2007). Using FMBV in early-onset IUGR, our group has recently demonstrated that frontal brain perfusion increases weeks before the MCA PI is significantly reduced in early-onset IUGR (Hernandez-Andrade et al., 2008). However, its behavior in term SGA fetuses has not been investigated before. In addition, normal reference ranges of cerebral blood perfusion have not been published before, which are required to investigate its clinical relevance under pathological conditions.

1.6 Aortic isthmus

The aortic isthmus (AoI) is the only arterial connection between the right ventricle, which mainly supplies the systemic and placental circulation, and the left ventricle, which essentially corresponding to the cerebral vascular network (Cruz-Martinez and Figueras, 2009). Increased aortic isthmus impedance indirectly reflects the shift of blood flow to the brain circulation as part of the fetal adaptation to hypoxia (Fouron, 2003) and has been associated with abnormal cardiac function(Makikallio et al., 2003, Girsen et al., 2007b) and higher risk of adverse perinatal(Del Rio et al., 2008) and neurodevelopmental outcome in childhood (Fouron et al., 2001, Fouron et al., 2005). Longitudinal studies have demonstrated that AoI PI becomes abnormal on average 1 week earlier than abnormal DV (Rizzo et al., 2008a, Figueras et al., 2009a) and therefore, has been proposed as promising parameters to improve fetal monitoring in severe early-onset IUGR although its integration into clinical management remains to be evaluated in future research. However, no studies have evaluated its changes and clinical relevance in term SGA fetuses.

1.7 Myocardial performance index

The myocardial performance index (MPI) is a novel method in fetal medicine that assesses both systolic and diastolic function by including the measurement of isovolumetric and ejection times and has demonstrated a correlation with the progression of cardiac dysfunction in early-onset IUGR, showing a correlation with biochemical markers as the severity of IUGR progresses(Ichizuka et al., 2005, Crispi et al., 2008). In early-onset IUGR, abnormalities in the DV, AoI and MPI appear according to a longitudinal sequence(Cruz-Martinez et al., 2010), increased MPI values are found in virtually all early-onset IUGR fetuses from the time of diagnosis, and on average they occur 2 and 3 weeks earlier than AoI and DV changes respectively, suggesting that MPI is highly sensitive to subtle forms of fetal hypoxia. Such high sensitivity, which constitutes a limitation for its clinical use to predict fetal death in early-onset IUGR(Hernandez-Andrade et al., 2009), might turn an advantage in SGA, since MPI could be used as a marker of fetal hypoxia, and thus of late-onset IUGR. In addition, although previous studies have constructed normal reference ranges of this parameter across gestational age, in such studies the number of cases included at each week of gestational age beyond 34 weeks was small and did not included cases above 39 weeks, which raises concern about the precision of these references at this extreme of the gestational age range and therefore, confirmation of normal MPI ranges in this period is desirable.

1.8 Ductus venosus

Evaluation of subclinical cardiac dysfunction in early-onset IUGR is already incorporated in the management of severe IUGR by means of the ductus venosus (DV) Doppler(Ghidini, 2007), particularly the finding of absent or reverse flow during the atrial contraction that is strongly associated with acidemia, myocardial necrosis and increased risk of perinatal death(Baschat et al., 2007, Baschat et al., 2003). However, DV abnormalities are often late signs of fetal compromise and no studies have evaluated its impact in term SGA fetuses with normal UA Doppler.

1.9 Relevance and justification of the research study

The impact of the identification of SGA fetuses at risk of adverse perinatal outcome of abnormal neurodevelopment is of clinical relevance and cannot be underestimated. SGA fetuses without signs of placental insufficiency as reflected in the umbilical artery Doppler account for up to 10% of the pregnant population by customized centiles (Figueras et al., 2007) represents about 400 000 cases/year in developed countries (MacDorman et al., 2010).

SGA fetuses are often managed by induction of labor (Larsen et al., 1992, Biran et al., 1994, McCowan et al., 2000a). However, labor induction in SGA carries a higher risk of fetal distress and emergency cesarean section(Severi et al., 2002), which in turn are associated with increased maternal and perinatal risks and high resource consumption (Lilford et al., 1990, Towner et al., 1999, Caughey et al., 2009). Since the identification of SGA fetuses with true growth restriction cannot be based on UA Doppler, further parameters allowing identification of late-onset IUGR at risk of adverse perinatal and neurodevelopmental outcome are required.

The identification of these babies at higher risk may might allow timely delivery, assist the decision-making process regarding labor induction to prevent long term neurodevelopmental and cardiovascular consequences and might result in a more efficient provision of resources at delivery.

2. HYPOTHESIS

Evaluation of fetal brain and cardiac Doppler parameters improves the identification of term, SGA fetuses with normal UA Doppler at risk of adverse perinatal outcome and abnormal neurobehavioral performance.

Specific hypothesis:

1. Cerebral blood perfusion is increased in SGA fetuses with normal umbilical artery Doppler as compared with normally grown fetuses.
2. Increased cerebral blood perfusion is earlier detected by means of the fractional moving blood volume using power Doppler ultrasound than by spectral Doppler indices.
3. Incorporation of fetal cardiac Doppler parameters might improve the identification of SGA fetuses with late-onset growth restriction.
4. Combination of power and spectral brain Doppler indices could improve the prediction of emergency cesarean section for intrapartum fetal distress after labor induction in term, SGA fetuses.
5. Abnormal cerebral blood perfusion discriminates SGA fetuses at risk of abnormal neurobehavioral performance with a better sensitivity than spectral Doppler indices.

3. OBJECTIVE

To evaluate the contribution of fetal brain and cardiac Doppler parameters in identifying SGA fetuses with late-onset intrauterine growth restriction at risk of emergency cesarean section for intrapartum fetal distress and abnormal neonatal neurobehavioral performance.

Specific objectives:

1. To establish normal reference intervals of fetal regional brain blood perfusion using power Doppler ultrasound as measured by FMBV.
2. To construct normal reference ranges of left modified myocardial performance index in near-term fetuses.
3. To compare the temporal sequence of fetal brain hemodynamic changes in near-term SGA fetuses, as measured by spectral-Doppler indices or by FMBV.
4. To evaluate the changes in myocardial performance index, aortic isthmus and ductus venosus in term, SGA fetuses with normal umbilical artery Doppler.
5. To explore whether a combination of brain Doppler parameters could improve the prediction of emergency cesarean section for fetal distress and neonatal acidosis after labor induction in term SGA fetuses.
6. To evaluate changes in cerebral blood perfusion and middle cerebral artery Doppler in term SGA fetuses and to explore their association with neonatal neurobehavioral performance.

4. METHODS

4.1 Study design

Between September 2007 and June 2010, a cohort was created of consecutive cases of suspected SGA singleton fetuses with normal umbilical artery Doppler(Arduini and Rizzo, 1990) born beyond 37 weeks of gestation, with confirmed birthweight below the 10th percentile according to local standards (Figueras et al., 2008b) at the Department of Maternal-Fetal Medicine, Hospital Clinic, Barcelona, Spain.

Exclusion criteria were: (i) congenital malformations and chromosomal abnormalities; and, (ii) umbilical artery PI above the 95th percentile (Arduini and Rizzo, 1990).

Controls were selected from our general population, individually matched with cases by gestational age at inclusion (± 1 weeks), corrected by first trimester ultrasound (Robinson and Fleming, 1975) and resulting in a neonatal birthweight between the 10th and 90th percentile(Figueras et al., 2008b). Women were offered to participate at a routine third-trimester ultrasound. All fetuses were followed until delivery to confirm the absence of any structural malformation by postnatal clinical examination.

4.2 Predictive variables

Epidemiological data

Maternal age, body mass index, smoking status, parity, socioeconomic level and ethnicity.

Perinatal data

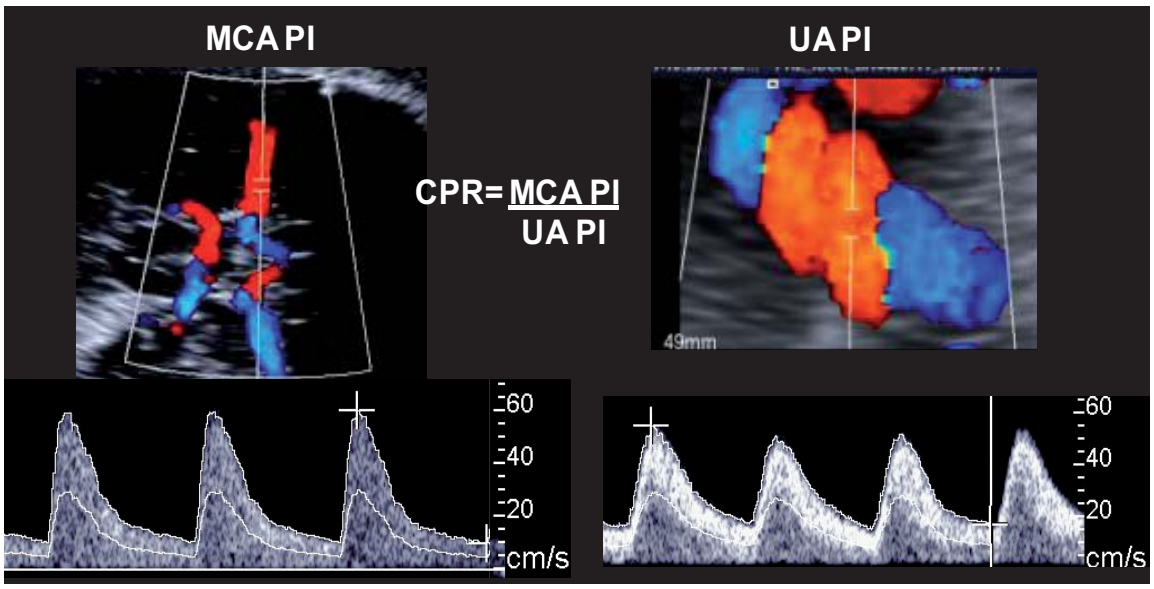
Last menstrual period corrected by the first trimester crown-rump length, pregnancy complications, gestational age at delivery, induction of delivery required and way of delivery.

Doppler ultrasound parameters

Prenatal Doppler ultrasound examinations were performed weekly using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) ultrasound machine equipped with a 6-2 MHz linear curved-array transducer. Doppler recordings were performed in the absence of fetal movements and voluntary maternal suspended breathing. Pulsed Doppler parameters were performed automatically from three or more consecutive waveforms, with the angle of insonation as close to 0 as possible. A high pass wall filter of 70 Hz was used to record low flow velocities and avoid artifacts. All studies were performed before the onset of labor.

Umbilical artery pulsatility index (PI) was performed from a free-floating cord loop. Normal UA was considered as a PI below the 95th percentile(Arduini and Rizzo, 1990).

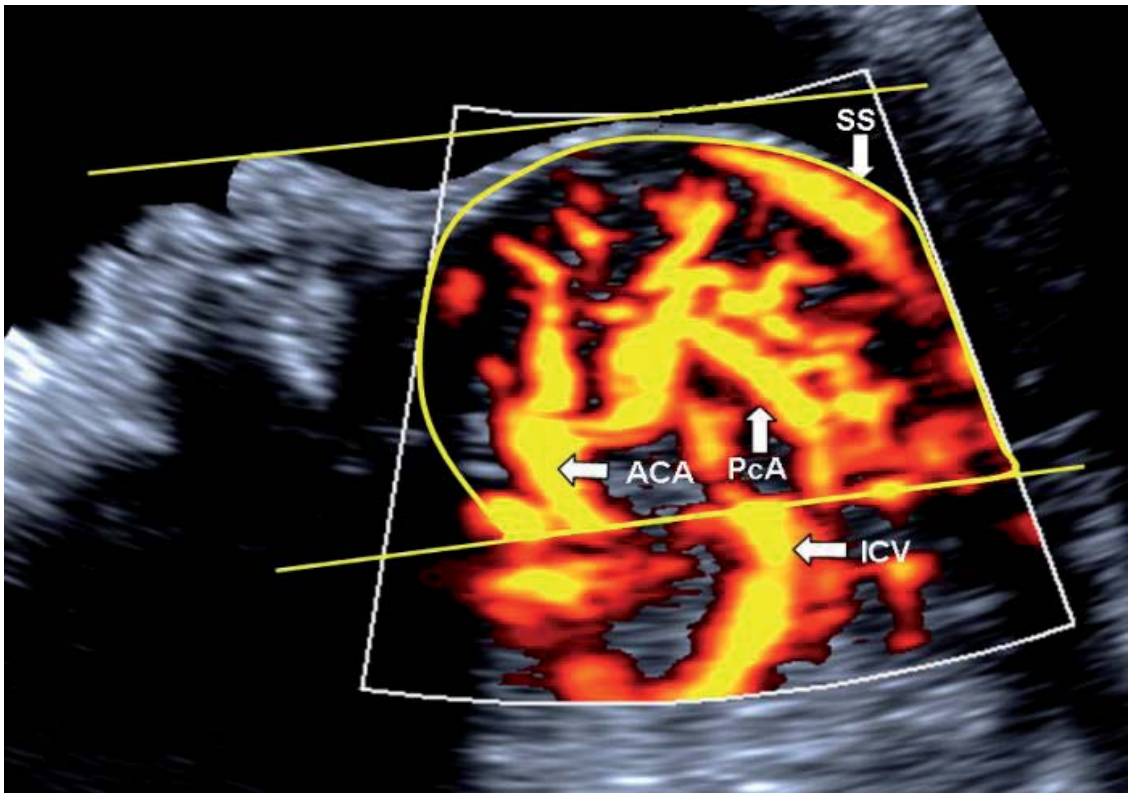
The ***middle cerebral artery*** PI was obtained in a transversal view of the fetal head, at the level of its origin from the circle of Willis. The cerebroplacental ratio was calculated as a ratio of the middle cerebral artery PI divided by the umbilical artery PI. The MCA PI and CPR values below the 5th percentile were considered indicative of cerebral blood flow redistribution(Baschat and Gembruch, 2003).



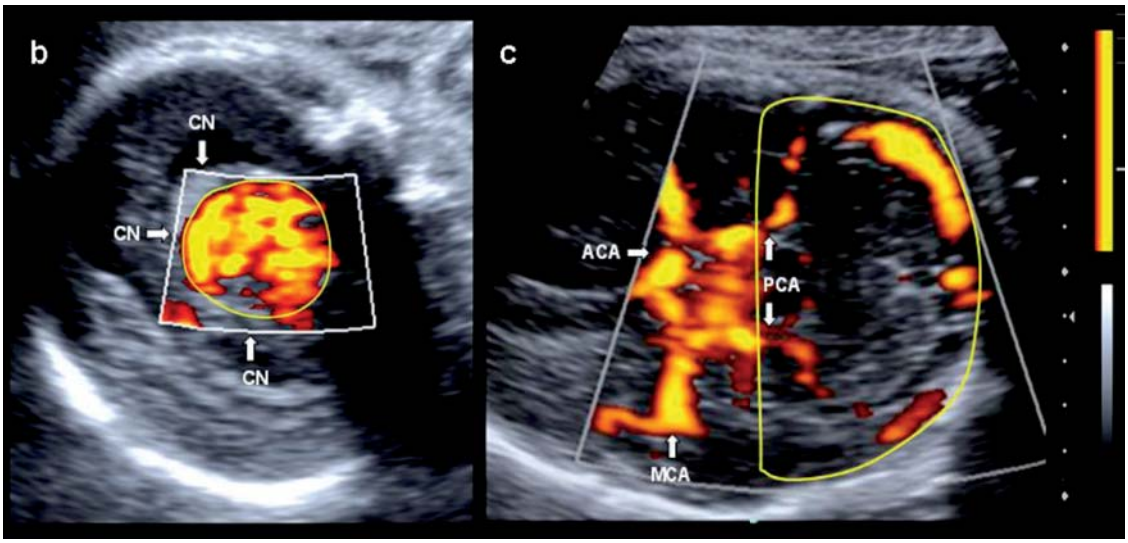
Using power Doppler ultrasound, ***cerebral blood perfusion*** was evaluated in the frontal lobe, basal ganglia and posterior brain. Five consecutive high-quality images with no artifacts were recorded using the following fixed setting: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1 and pulsed repetition frequency of 610 Hz.

All images were examined off-line and FMBV was estimated according with the methodology previously described (Jansson et al., 2003). The mean FMBV from all 5 images was considered as representative for that specific case and expressed as percentage.

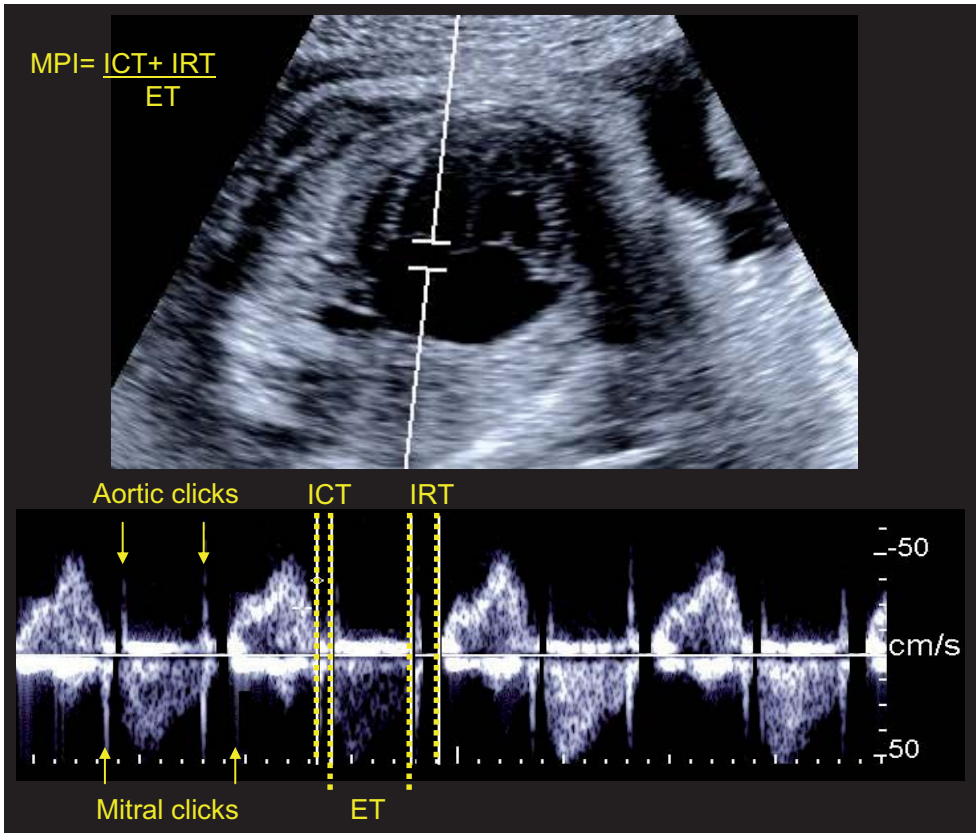
The three regions of interest (ROI) were delimited as described elsewhere (Hernandez-Andrade et al., 2007). For the frontal area, in a mid sagittal view of the fetal brain, the power Doppler color box was placed to include all the anterior part of the brain. The ROI was delimited anteriorly by the internal wall of the skull, inferiorly by the base of the skull and posteriorly by an imaginary line drawn at 90° from the origin of the anterior cerebral artery (ACA) and parallel to an imaginary line in the front of the face and crossing at the origin of the internal cerebral vein (ICV).



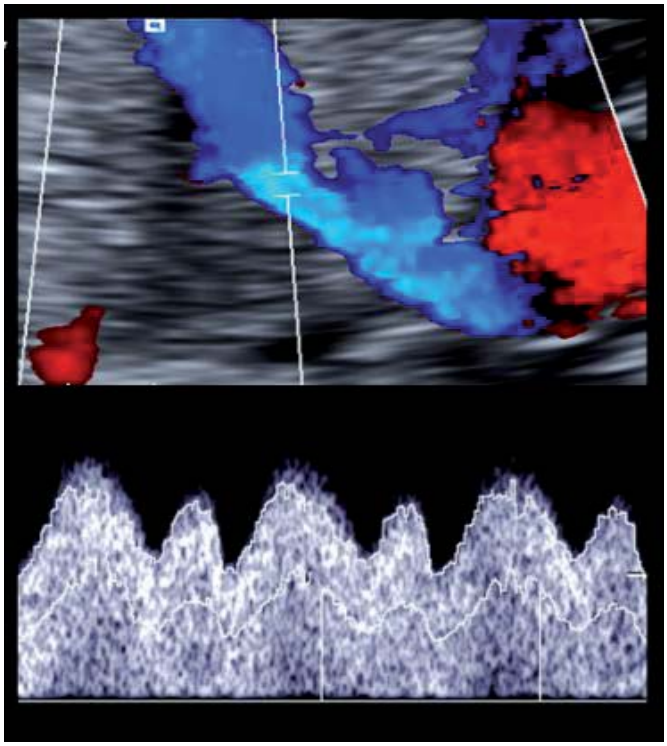
For the basal ganglia (b), in a mid-parasagittal view of the fetal head, the ROI was delimited by the head, body and tail of the caudate nucleus (CN) and inferiorly by the lenticular nucleus. For the posterior brain (c), in a transverse plane of the fetal head, the ROI was delimited anteriorly by the base of the cerebellar hemispheres and posteriorly by the fetal skull. Increased brain perfusion was considered as FMBV values above the 95th percentile.



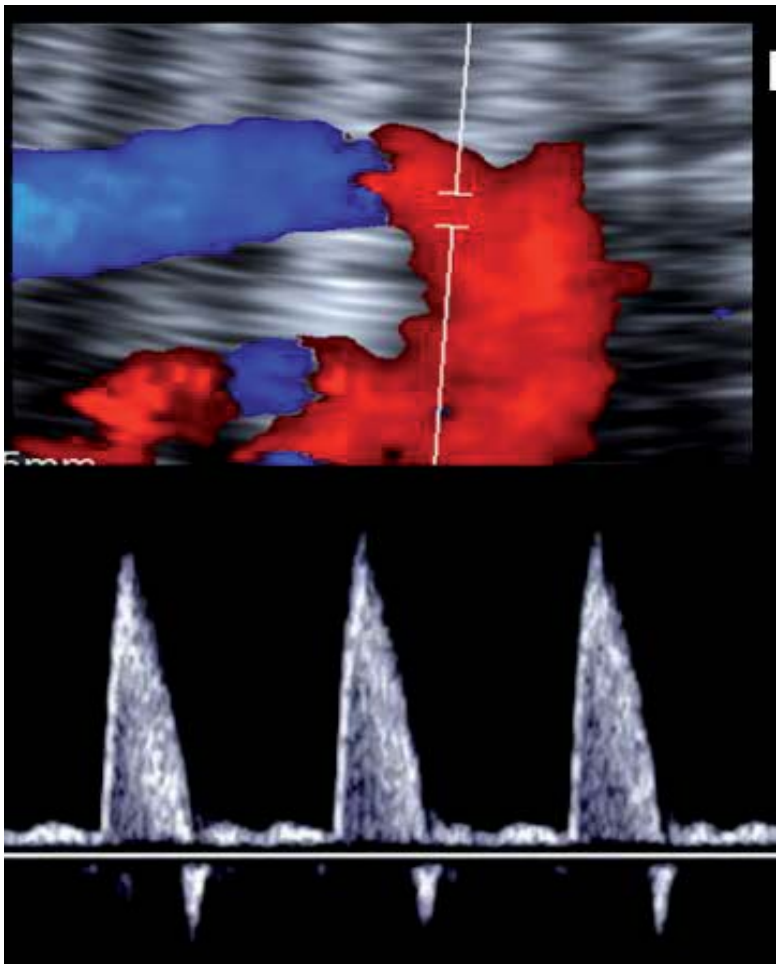
The ***Myocardial performance index*** was measured as previously described by Hernandez-Andrade et al.(Hernandez-Andrade et al., 2005) In a cross-sectional view of the fetal thorax, in an apical projection and at the level of the four-chamber view of the heart, the Doppler sample volume was placed to include both the lateral wall of the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves can be clearly visualized. Spectral Doppler images were obtained using a sample volume of 3-4mm, a gain level of 60, a Doppler sweep velocity of 8, and with the E/A waveform always displayed as positive flow. The isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) were calculated using the beginning of the mitral and aortic valves clicks as landmarks and the MPI was calculated as follows: (ICT+IRT)/ET. Increased MPI was defined as those values above the 95th centile.



Ductus venosus was performed in a mid-sagittal or a transverse section of the fetal abdomen, positioning the Doppler gate at its isthmic portion.



The ***Aortic isthmus*** PI was measured either in a sagittal view of the fetal thorax with clear visualization of the aortic arch, placing the gate a few millimetres beyond the origin of the left subclavian artery; or in a cross-sectional view of the fetal thorax, at level of the three vessels and trachea view, placing the gate just before the convergence of the AoI and the arterial duct (Del Rio et al., 2005, Rizzo et al., 2008).



DV and aortic isthmus pulsatility indices were converted into z-scores according to published normal references and considered as abnormal with values above the 95th percentile (+1.645 z-scores)(Del Rio et al., 2006, Hecher et al., 1994) in two consecutive observations (24-hour apart).

4.3 Management and outcome variables

Labor induction was performed at term (≥37 weeks) for all SGA cases by cervical ripening with a slow release prostaglandin E2 vaginal pessary (10 mg). If the onset of labor did not occur within 12 hours, oxytocin induction was performed. All deliveries were attended by a staff obstetrician blinded to the results of the brain and cardiac Doppler parameters evaluated in this study.

Neonatal data: Gender, gestational age, birth weight, birth weight percentile, Apgar score at 1 and 5 minutes, cord arterial and venous birth pH, base excess, pO_2, days in neonatal intensive care, mechanical ventilation, need for O_2, morbidity, and mortality.

Adverse perinatal outcome was defined as the presence of any of the following neonatal measures:

a) *Low Apgar score*. A 5-minute Apgar score below 7.0 assigned by the attending neonatologist.
b) *Fetal distress* (FD) was defined according to the American College of Obstetricians and Gynecologists as a nonressuring fetal heart rate trace, with a fetal scalp pH below 7.20, or sustained fetal bradycardia during labor monitoring(Preboth, 2000). Cases where cervical conditions did not allow fetal scalp sampling, were considered for cesarean section for fetal distress if persistence of abnormal tracing after pessary withdrawal and 10-min of intravenous infusion of ritrodine (200 μg/min).
c) Metabolic acidosis was defined as the presence of an umbilical artery pH below 7.15 and base excess>12mEq/L in the newborn.(Gregg and Weiner, 1993)

Neurobehavioral assessment:

The Neonatal Behavioral Assessment Scale (NBAS) was prospectively performed in all cases and controls at 40-week (±1) corrected age by one of three observers accredited by The Brazelton Institute (Harvard Medical School, Boston, USA). The observers were blinded to the study group and to the Doppler status. The examination consisted of 6 behavioral areas rated on a 1 to 9 scale where 9 is the best performance for some areas and for others this is represented by the central score of 5 (Brazelton, 1995). With the newborn between two feedings, in a small and quiet room, semi-dark, with a temperature between 22 to 27°C and in the presence of at least one parent, the following areas were analyzed: social-interactive (which include response to visual and acoustic stimuli), organization of state (which include peak of excitement, rapidity of build-up, irritability and lability of states) and motor (which include general tone, motor maturity, pull-to-sit, defensive movements and level of activity). Following a recent report by the original authors of the NBAS, individual items were clustered to assess the attention capacity (which includes alertness, quality of alert responsiveness and cost of attention) (Sagiv et al., 2008). The behavioral items were converted into percentiles according to normal curve references for our population (Costas Moragas et al., 2007), and each area was considered abnormal at a score below 5th percentile.

4.4 Ethical approval

The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women.

4.5 Statistical analysis

We are expecting differences between SGA fetuses and controls in the brain and cardiac Doppler parameters above 10%. For a given 5% alpha-error, 80% power and β=2%, meaning a sample size of 60 patients in each study group.

Student's t-test or One-way ANOVA and Pearson Chi-squared test or exact Fisher test were used to compare quantitative and qualitative data, respectively. The Mc Nemar test was used to compare pair group proportions.

Normality ranges were constructed by the regression model described by Royston and Wright (Royston and Wright, 1998) or LMS methodology (Cole and Green, 1992, Bartha et al., 2009) according to the presence of normal or skewness in the distribution of the studied parameters, respectively.

For the regression model, normal distribution of the studied variables and its individual components were checked with the Shapiro-Francia W-test, and a natural logarithmic transformation of the data was used if necessary. Separate cubic, quadratic and linear regression models were fitted to estimate the relationship between the studied variables and gestational age (GA). Standard deviation (SD) curves as functions of GA were calculated by means of a polynomial regression procedure of absolute residuals for each measurement of interest. The 5^{th} and 95^{th} percentiles for each GA were calculated as follows: mean ± 1.645 x SD. Normal distribution of the resulting model was verified by obtaining normal probability plots of the z-scores overall and for each gestational age.

For the LMS method, the optimal power to obtain normality was calculated for each age group and the trend summarized by a smooth (L) curve.

Trends in the mean (M) and coefficient of variation (S) are similarly smoothed. The resulting L, M and S curves contain the information to draw any centile curve, and to convert measurements into exact SD scores. Degrees of freedom for each curve (L, M and S) were selected according to changes in the model deviance. Normal distribution of the resulting model was verified by obtaining normal probability plots of the z-scores overall and for each gestational age.

The LMS chart maker software was used (LMS Chart maker Pro, version 2.3, Medical Research Council, UK).

The longitudinal changes were analyzed by Kaplan-Meier survival analysis, in which the endpoint was defined as an abnormal Doppler value.

The association between abnormalities in the fetal Doppler parameters and the risk of emergency cesarean delivery for non-reassuring fetal status and metabolic acidosis was analyzed by multiple simple logistic regression (for independent data) or conditional logistic regression (for paired data) adjusted by estimated fetal weight percentile and gestational age at birth.

Then, a predictive model was constructed using the Decision Tree Analysis algorithm for the occurrence of cesarean section (CS) and emergency CS for FD. The decision tree was developed using the Classification and Regression Trees CHAID method (Quick, Unbiased and Efficient Statistical Tree), which generates binary decision trees with the P inset at 0.05 (Bonferroni-adjusted for multiple comparisons) and a cut-off selected automatically for all the parameters included(Shih, 1999). The classification and regression tree was constructed by splitting subsets of the dataset using all predictor variables to create two child nodes repeatedly. The best predictor was chosen using a variety of impurity and diversity measures. The stopping rules for the iterative process were that the tree should have a maximum of three levels, a minimum of ten cases were to be present for a split to be calculated and any given split should not generate a group with less than five cases.

Following standard methodology, the association between brain Doppler and neurobehavioral outcome was analyzed by multiple linear or logistic regression adjusted by potential confounders such as smoking during pregnancy (no smoking; 1-9 cigarettes/day; 10^{+} cigarettes/day), labor induction, mode of delivery (cesarean section vs. vaginal delivery), gestational age at birth, gender and postnatal days at evaluation (Boatella-Costa et al., 2007, Brazelton, 1995, Lundqvist and Sabel, 2000) . All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 18.0, SPSS Inc., Chicago, IL, USA) statistical software.

5. PUBLISHED STUDIES

The projects included in this thesis belong to the same research line leading to six articles already published or submitted for publication in international journals:

1. **Cruz-Martinez R**, Figueras F, Hernández-Andrade E, Benavides-Serralde A, Gratacos E. Normal references ranges of fetal regional cerebral blood perfusion as measured by Fractional Moving Blood Volume.
   Ultrasound Obstet Gynecol 2011; 37:196-201.

2. **Cruz-Martinez R**, Figueras F, Hernández-Andrade E, Oros D, Gratacos E. Normal reference ranges of left myocardial performance index in near-term fetuses.
   Fetal Diagn Ther 2010, submitted

3. **Cruz-Martinez R**, Figueras F, Hernández-Andrade E, Puerto B, Gratacos E. Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by Fractional Moving Blood Volume.
   Am J Obstet Gynecol 2010;203:42.e1-6.

4. **Cruz-Martinez R**, Figueras F, Hernández-Andrade E, Oros D, Gratacos E. Changes in myocardial performance index, aortic isthmus and ductus venosus in term, small-for-gestational age fetuses with normal umbilical artery Doppler.
   Ultrasound Obstet Gynecol 2011, Epub ahead of print.

5. **Cruz-Martinez R**, Figueras F, Hernández-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for non-reassuring fetal status in term, small-for-gestational age fetuses.
   Obstet Gynecol 2011;117:618-26.

6. **Cruz-Martinez R,** Figueras F, Oros D, Meler E, Padilla N, Hernández-Andrade E, Gratacos E. Cerebral blood perfusion and neurobehavioral performance in full term small for gestational age fetuses.
   Am J Obstet Gynecol 2009 Nov; 201(5):474.e1-7.

STUDY 1

Normal reference ranges of cerebral blood perfusion as measured by Fractional Moving Blood Volume.

Cruz-Martinez R, Figueras F, Hernández-Andrade E, Benavides-Serralde A, Gratacos E.

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Normal reference ranges of fetal regional cerebral blood perfusion as measured by fractional moving blood volume

R. CRUZ-MARTINEZ*, F. FIGUERAS*, E. HERNANDEZ-ANDRADE*†, A. BENAVIDES-SERRALDE*† and E. GRATACOS*

**Fetal and Perinatal Medicine Research Group, Department of Maternal-Fetal Medicine Hospital Clinic-IDIBAPS, University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBERER), Barcelona, Spain; †Department of Maternal-Fetal Medicine, National Institute of Perinatal Medicine, Mexico City, Mexico*

KEYWORDS: basal ganglia; cerebral blood perfusion; fractional moving blood volume; frontal lobe; posterior brain; power Doppler

ABSTRACT

Objectives *To establish normal reference intervals of fetal regional brain blood perfusion using power Doppler ultrasound as measured by fractional moving blood volume (FMBV).*

Methods *A cohort of consecutive singleton normally grown fetuses was selected including at least 12 fetuses for each completed week of gestation between 24 and 41 weeks. Cerebral blood perfusion was estimated using conventional power Doppler ultrasound in the following brain regions: frontal area, basal ganglia and posterior brain. Five consecutive good-quality images were recorded in each area and the region of interest was delineated offline. The FMBV was quantified as the average of all images and expressed as a percentage. Normal reference ranges were constructed by means of the LMS (lambda-mu-sigma) method.*

Results *A total of 230 fetuses were included. The median gestational age at evaluation and at delivery was 33.1 (range, 24.0–41.0) and 39.7 (range, 34.9–42.3) weeks, respectively. From 24 to 41 weeks' gestation, the mean FMBV increased from 13.21 to 14.97% in the frontal area, 11.17 to 14.86% in the basal ganglia and 4.83 to 6.70% in the posterior brain.*

Conclusions *Normal data of fetal cerebral blood perfusion in the frontal area, basal ganglia and posterior brain are provided, which could be of clinical use in the assessment of fetal brain circulation.*

INTRODUCTION

In most children with neurological problems brain damage occurs before birth[1]. One of the main risk factors for brain damage is intrauterine growth restriction (IUGR), which affects 1–3% of all pregnancies[2]. Growth restricted fetuses show a so-called 'brain sparing' effect during pregnancy, whereby more blood is directed to certain brain regions. Abnormal fetal brain circulation has been associated with long-term abnormal neurodevelopment[3,4], consequently evaluation of hemodynamic changes in the brain is performed in order to plan fetal surveillance and make clinical decisions.

Clinically, the standard parameter for assessing fetal brain circulation is middle cerebral artery (MCA) pulsatility index (PI), and brain sparing is diagnosed when it is decreased[5]. However, hemodynamic evaluation by conventional spectral Doppler does not directly reflect changes in tissue perfusion because it has a low sensitivity for measuring subtle changes in blood movement within the small vessels[6–8]. In an attempt to increase the sensitivity of spectral Doppler evaluation, cerebral blood perfusion has been estimated using three-dimensional (3D) power Doppler ultrasound (PDU)[9–12], and it has been shown that PDU may provide more sensitive information about changes in cerebral blood perfusion. However, these methods represent estimates that are subject to substantial bias due to a lack of correction for attenuation and depth[13–16].

More recently, fractional moving blood volume (FMBV), a quantitative methodology that compensates for common estimation errors[17,18], has been validated against gold standards for fetal evaluation[19]. This emerging methodology has been used to demonstrate that cerebral blood perfusion increases earlier and in a higher proportion of growth restricted fetuses than do other spectral Doppler indices[20,21] and is associated with brain maturation disruption[22]. However, normal reference ranges of these parameters across gestational age have not yet been published. The aim of our study

Correspondence to: Dr F. Figueras, Maternal-Fetal Medicine Department, Hospital Clinic, University of Barcelona, Sabino de Arana 1, 08028 Barcelona, Spain (e-mail: ffiguera@clinic.ub.es)

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was to construct gestational age-based reference intervals for fetal regional cerebral blood perfusion in the frontal area, basal ganglia and posterior brain as measured by FMBV.

SUBJECTS AND METHODS

Between December 2008 and September 2009, a prospective cohort was created by recruiting, at the time of the routine third-trimester ultrasound scan, consecutive singleton fetuses that had estimated fetal weight between the 10th and 90th percentiles according to local standards[23]. Included were at least 12 cases for each gestational week between 24 and 41 weeks, corrected by first-trimester ultrasonography[24]. Exclusion criteria were the presence of congenital malformations and chromosomal abnormalities. All fetuses were followed until delivery to confirm the absence of any structural malformation by postnatal clinical examination and those cases with a birth weight below the 10th or above the 90th centile were not subsequently excluded. The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women.

Prenatal Doppler ultrasound examinations were performed using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) ultrasound machine equipped with a 6–2-MHz linear curved-array transducer, by one of two experienced operators (R.C.M. or E.H.A). Using PDU, cerebral blood perfusion was evaluated in the frontal area, basal ganglia and posterior brain. Five consecutive high-quality images with no artifacts were recorded using the following fixed settings: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1 and pulsed repetition frequency of 610 Hz. All images were examined offline and FMBV was estimated according to the methodology previously described by Hernandez-Andrade *et al.*[25]. The mean FMBV from all five images was considered as representative for that specific case and expressed as a percentage.

The three regions of interest (ROIs) were delineated as described elsewhere[25]. For the frontal area, in a midsagittal view of the fetal brain the power Doppler color box was placed to include all the anterior part of the brain. The ROI was delimited anteriorly by the internal wall of the skull, inferiorly by the base of the skull and posteriorly by an imaginary line drawn at 90° from the origin of the anterior cerebral artery and parallel to an imaginary line in the front of the face and crossing at the origin of the internal cerebral vein (Figure 1a). For the basal ganglia, in a parasagittal view of the fetal head, the ROI was delimited by the head, body and tail of the caudate nucleus and inferiorly by the lenticular nucleus (Figure 1b). For the posterior brain, in a transverse plane of the fetal head, the ROI was delimited anteriorly by the base of the cerebellar hemispheres and posteriorly by the fetal skull (Figure 1c). All studies were performed before the onset of labor and only one set of measurements for each patient was included in the analysis. Induction of labor was scheduled for cases reaching 42 weeks' gestation or with premature rupture of membranes by cervical ripening. Delivery was attended by a staff obstetrician.

Statistical analysis

Normal ranges were constructed by the LMS (lambda-mu-sigma) method[26]. In brief, the LMS method summarizes the changing distribution by three curves representing the skewness expressed as a Box–Cox power (L), the median (M) and coefficient of variation (S). The resulting L, M and S curves contain the information needed to draw any percentile curve, and to convert measurements into exact SD scores. Degrees of freedom for each curve (L, M and S) were selected according to changes in the model deviance. Normal distribution of the resulting model was verified by obtaining normal probability plots of the *Z*-scores overall and for each gestational age. A table reporting the mean and the 90% interval of prediction (5th and 95th centiles) for each of the measurements was created. The LMS chart maker software was used (LMS Chart maker Pro, version 2.3, Medical Research Council, UK).

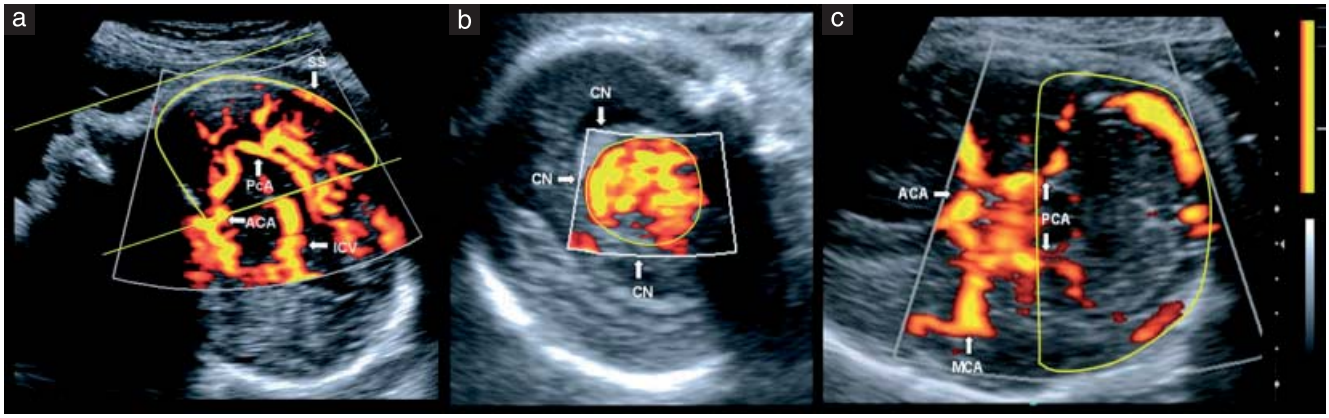

Figure 1 Power Doppler ultrasound images showing the regions of interest of the fetal brain, from where cerebral blood perfusion was estimated in the frontal area (a), basal ganglia (b) and posterior brain (c). ACA, anterior cerebral artery; CN, caudate nucleus; ICV, internal cerebral vein; MCA, middle cerebral artery; PcA, pericallosal artery; PCA, posterior cerebral artery; SS, sagittal sinus.

RESULTS

During the study period a total of 238 fetuses were included. Cerebral blood perfusion in the basal ganglia and posterior brain were successfully obtained in all examinations, while frontal tissue perfusion could not be obtained in eight cases above 38 weeks' gestation. Thus, a final population of 230 fetuses was analyzed, in whom the median gestational age at inclusion and at delivery was 33.1 (range, 24.0–41.4) and 39.7 (range, 34.9–42.3) weeks, respectively. Maternal characteristics and perinatal outcomes are summarized in Table 1.

For the frontal area the degrees of freedom used in fitting the cubic splints were 5, 12 and 6 for the L, M and S curves, respectively; the values were 5, 10 and 7, and 4, 10 and 8, for the basal ganglia and posterior brain regions, respectively.

Table 1 Clinical characteristics of the study population ($n = 230$)

Characteristic	*Median (range) or %*
Gestational age at inclusion (weeks)	33.1 (24.0–41.4)
Maternal age (years)	31.1 (17.6–43.6)
Primiparous	57.7
Non-Caucasian ethnicity	15.8
Labor induction	25.9
Mode of delivery	
Spontaneous	62.5
Vacuum or forceps	20.2
Cesarean	17.3
Gestational age at delivery (weeks)	39.7 (34.9–42.3)
Birth weight (g)	3183 (2250–4510)
Birth-weight centile	40.5 (7–96)

Table 2 shows the gestational-age-related reference ranges for regional cerebral blood perfusion in the three areas explored. The basal ganglia showed the highest FMBV values, followed by the frontal area and posterior brain. Figure 2 depicts the estimated mean and percentile curves for each area studied across gestational age. With advancing gestation, brain tissue perfusion slightly increased in the three evaluated areas. From 24 to 41 weeks' gestation, the mean FMBV increased from 13.21 to 14.97% in the frontal area, 11.17 to 14.86% in the basal ganglia and 4.83 to 6.70% in the posterior brain, respectively.

DISCUSSION

No studies so far have evaluated quantitatively the sequence of changes in cerebral blood perfusion in different regions of the fetal brain as assessed by FMBV in relation to gestational age. In this study we provide normal references in percentiles for fetal cerebral blood perfusion during pregnancy and demonstrate differences in FMBV values between the three regions of the fetal brain studied across gestational age.

During the past three decades, the gold standard for evaluation of fetal brain circulation has been conventional spectral Doppler ultrasound. However, in comparison with PDU, spectral Doppler has the limitation of being angle-dependent and susceptible to aliasing[6–8]. In addition, evaluation of a single vessel has a fundamental limitation: since the territory perfused by any vessel is ill-defined, changes that might be occurring in specific brain areas cannot be selectively targeted[6]. Studies based on PDU may overcome this problem since they allow ROIs

Table 2 Normal references values of cerebral blood perfusion as measured by fractional moving blood volume (FMBV)

	Cerebral blood perfusion by FMBV (%)								
	Frontal area			*Basal ganglia*			*Posterior brain*		
GA (weeks)	*p5*	*Mean*	*p95*	*p5*	*Mean*	*p95*	*p5*	*Mean*	*p95*
24	5.39	13.21	24.38	5.32	11.17	19.86	2.24	4.83	9.21
25	5.69	13.23	24.39	5.33	11.39	20.35	2.27	4.90	9.36
26	5.95	13.24	24.39	5.34	11.61	20.83	2.29	4.96	9.53
27	6.18	13.45	24.39	5.36	11.82	21.32	2.32	5.03	9.71
28	6.38	13.56	24.40	5.37	12.04	21.82	2.36	5.11	9.91
29	6.56	13.66	24.41	5.39	12.26	22.31	2.39	5.19	10.11
30	6.72	13.77	24.41	5.39	12.48	22.81	2.42	5.27	10.31
31	6.86	13.88	24.43	5.41	12.69	23.31	2.46	5.36	10.51
32	6.99	13.99	24.46	5.41	12.91	23.81	2.49	5.44	10.73
33	7.10	14.10	24.50	5.43	13.13	24.31	2.53	5.53	10.96
34	7.20	14.21	24.55	5.43	13.34	24.82	2.58	5.64	11.22
35	7.28	14.32	24.62	5.45	13.56	25.32	2.63	5.77	11.53
36	7.36	14.43	24.69	5.45	13.78	25.83	2.70	5.91	11.88
37	7.43	14.54	24.78	5.46	13.99	26.35	2.76	6.06	12.23
38	7.49	14.65	24.88	5.46	14.21	26.86	2.83	6.21	12.60
39	7.54	14.76	25.00	5.46	14.43	27.38	2.89	6.37	12.98
40	7.59	14.86	25.14	5.46	14.64	27.89	2.96	6.53	13.37
41	7.63	14.97	25.30	5.47	14.86	28.41	3.03	6.70	13.77

GA, gestational age; p5, 5th centile; p95, 95th centile.

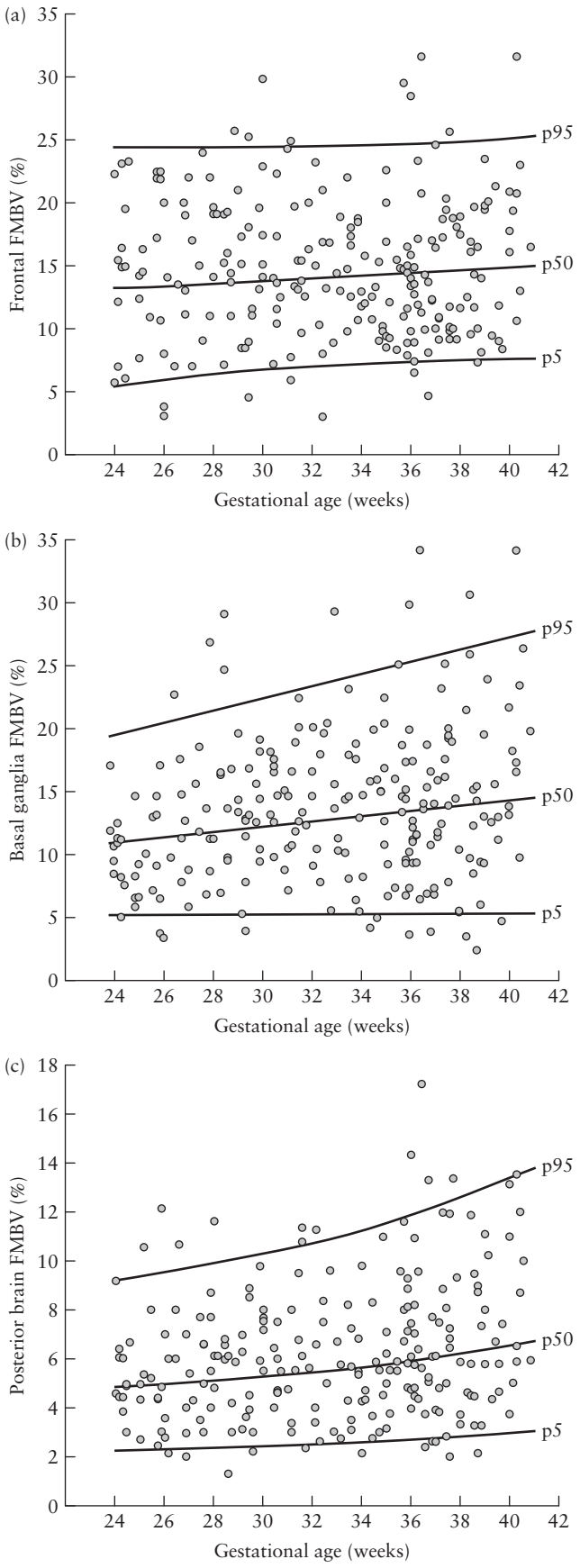

Figure 2 Plots of cerebral blood perfusion in the fetal brain against gestational age: (a) frontal area; (b) basal ganglia; and (c) posterior brain. FMBV, fractional moving blood volume; p5, 5th centile; p50, 50th centile; p95, 95th centile.

to be defined. This method assesses the amplitude of the acoustic signals by counting the number and intensity of color pixels within a given region, which allows inference of the number of moving blood cells and thus blood flow within the region. In addition, the method has a higher sensitivity than does spectral Doppler for the detection of low-velocity blood flow[8].

Several indirect methods have been applied for the estimation of blood perfusion using PDU. The most widely reported is a 3D method described by Pairleitner *et al.*[27] that assesses the signal intensity within a volume of interest using a spherical model using virtual organ computer-aided analysis (VOCAL™) software to quantify three vascular indices. However, these indices reflect vascularity and flow intensity but not true blood tissue perfusion[28]. Moreover, as this method quantifies only the crude intensity values without standardization, it is prone to bias due to attenuation effects, field depth, erythrocyte density (rouleaux effects) and machine settings[13–15]. To overcome these limitations, FMBV has been described as a two-dimensional method that identifies signals coming from 'true blood' and excludes those from artifacts or tissue movements by a double normalization process[16–18,29]. This technique has shown an excellent correlation with gold standards in the estimation of true tissue blood flow in animal experiments[19]. By analyzing several consecutive images, the technique allows estimation of brain perfusion at different points in the cardiac cycle. Thus, the method has shown good reproducibility in the assessment of brain perfusion in human fetuses in the three regions included in this study, with a variability below 10% and a high degree of inter- and intraobserver agreement (intraclass correlation coefficient above 0.9)[25].

In this study the relative values of brain tissue perfusion increase slightly through the third trimester. These findings are consistent with those of previous studies using cerebral spectral Doppler ultrasound, which have reported decreasing impedance in the MCA and anterior cerebral artery as gestation progresses[30–33]. Similarly, other studies using 3D-PDU have qualitatively assessed fetal cerebral blood perfusion and reported that brain perfusion values increase with gestational age[9–12]. In agreement with our previous study[25], the FMBV values obtained from the same evaluated brain regions appear different between areas, with the lowest values in the posterior brain, followed by the basal ganglia and frontal area. These differences could be explained by the fact that FMBV assesses blood movement within an ROI that includes small and large blood vessels. However, the highest individual values were observed in the basal ganglia area, in which the large blood vessels are smaller than are those in the other two studied areas. A study comparing the FMBV algorithm used in this study with one in which the signals from the large vessels are excluded is required.

Although in clinical practice brain redistribution is based on the presence of a low MCA-PI[5], previous longitudinal studies have reported that fetuses with severe

early-onset IUGR with Doppler signs of placental insufficiency had increased brain tissue perfusion from the earlier stages of fetal deterioration and long before an abnormal MCA-PI could be observed[21]. In addition, in near-term small-for-gestational-age (SGA) fetuses with normal umbilical artery, brain sparing was detected earlier and in a higher proportion of cases using cerebral blood perfusion as measured by FMBV than by other spectral Doppler indices such as those of the MCA and anterior cerebral artery and the cerebroplacental ratio[20]. In a recent study, we demonstrated that 40% of SGA fetuses present increased brain tissue perfusion and that this finding is associated with a higher risk of abnormal neonatal neurobehavioral performance in social-interactive organization, organization of state and attention capacity, indicating disrupted brain maturation[22].

The reference values described here provide physiological insights into the normal evolution of the human brain in pregnancy and could have clinical implications in the future for the early detection of increased brain blood perfusion, possibly providing a sensitive method of identifying fetuses with signs of hypoxia and with a higher risk of abnormal neurodevelopment at much earlier stages than current clinical tests[20]. This information could be of clinical relevance for enabling timely delivery and preventing long-term consequences.

There are still limitations to the widespread application of tissue perfusion measurements in pregnancy. Firstly, estimation of brain-tissue perfusion in the frontal area remains difficult at advanced gestational ages. Thus, while – in this study – the basal ganglia and posterior brain could be examined in all cases independently of the position of the fetal head, frontal perfusion could not be evaluated in a few cases at advanced gestational age. The sagittal view of the fetal head required to evaluate frontal area perfusion offers a good acoustic window with a clear observation of different structures of the fetal brain. However, at later gestational ages, normally above 37 weeks, there is an intrinsic difficulty in obtaining this plane correctly, mainly due to the posterior position and the degree of engagement of the fetal head into the pelvis in term fetuses. On the other hand, in breech presentation or in preterm fetuses it is usually easily obtained. Further studies are underway in an attempt to identify easier insonation planes. Secondly, the clinical application is also limited because current ultrasound equipment does not yet incorporate FMBV algorithms for the automatic calculation of tissue perfusion. We recognize that the time consumed in the offline image process in estimating FMBV is also a limitation (approximately 5 min per evaluated area). However, some of the other tools that are integrated into currently available commercial devices have substantial limitations in the estimation of perfusion due to a lack of correction for attenuation and depth[14]. A third important limitation is the need for precise setting definitions in order to allow the algorithm to establish the right inferences. This bottleneck requires the development of algorithms that are independent of these constraints and this research is also underway. Finally, the relative broadness of the reported normal ranges may limit their clinical applicability. Despite the high variability in what could be considered normal perfusion, the 5% of fetuses with the highest perfusion (i.e. those with a potential risk of brain maturation disruptions) can nonetheless be selected using the normal ranges.

In conclusion, cerebral blood perfusion as measured by FMBV shows slight changes across gestational age and differs between fetal brain regions. These data could be used as a reference for further studies in the evaluation of fetal brain blood perfusion in pathological conditions.

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STUDY 2

Normal reference ranges of fetal modified myocardial performance index in near term fetuses.

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Normal reference ranges of left modified myocardial performance index in near term fetuses between 34-42 weeks of gestation.

Rogelio Cruz-Martinez, M.D.[1]; Francesc Figueras, PhD[1]; Daniel Oros[1]; Edgar Hernandez-Andrade, PhD[1,2]; M.D; Eduard Gratacos, PhD[1].

[1]Fetal and Perinatal Medicine Research Group, Department of Maternal-Fetal Medicine Hospital Clinic-IDIBAPS, University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain. [2] Department of Maternal-Fetal Medicine, National Institute of Perinatal Medicine, Mexico City, Mexico (INPerIER).

Short Title. MPI normality in term fetuses.

Correspondence to:

Rogelio Cruz Martinez
Maternal-Fetal Medicine Department
Hospital Clinic, University of Barcelona
Sabino de Arana 1, 08028 Barcelona
Spain
Telephone: +34 93 227 5400,
Fax: +34 (0) 93 227 9336
e-mail: jcruz1@clinic.ub.es

ABSTRACT

Objective: To establish normal reference intervals of fetal left modified myocardial performance index (MPI) in near term fetuses.

Methods: A cohort of consecutive singleton normally grown fetuses was created including 30 fetuses for each completed week of gestation between 34 and 42 weeks. The isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET) were calculated using the clicks of the mitral and aortic valves as landmarks, and the MPI was calculated as follows: (ICT+IRT)/ET. Normal reference ranges for the MPI and its individual components were constructed by means of regression analysis of the mean and standard deviation against gestational age.

Results: A total of 245 fetuses were included. The median gestational ages at evaluation and delivery were 37.2 (range, 34.0-42.0) and 39.8 (range, 35.4-42.1) weeks, respectively. From 34 to 42 weeks of gestation, the mean MPI showed a progressive increase from 0.46 to 0.53. While the mean ICT and IRT values increased throughout gestational age from 31 to 35ms and from 42 to 50ms, respectively; the ET showed a progressive decreased from 170 to 159ms.

Conclusion: Normative references of left MPI from 34 to 42 weeks of gestation are provided, which could be useful in the assessment of cardiac function in near term fetuses.

Key words: *Myocardial performance index, TEI index, MPI, normal ranges.*

INTRODUCTION

Cardiovascular evaluation is becoming increasingly important for the study of several fetal conditions [1,2]. The incorporation of cardiovascular parameters for prenatal detection of cardiac dysfunction has long constituted an important goal in clinical practice and fetal medicine research [3]. Myocardial performance index (MPI), a quantitative index that expresses the quotient of the duration of isovolumetric contraction and relaxation times divided by the ejection time, has gained acceptance for the assessment of fetal cardiovascular function. The index has been used to demonstrate cardiac dysfunction in fetuses with early-onset intrauterine growth restriction [4-7], complications of monochorionic twins [8,9], congenital diaphragmatic hernia [10] and diabetic pregnancies [11,12].

Over recent years several studies have described methods to improve the reproducibility of MPI in fetuses by including the clicks of the aortic and mitral valves as landmarks to define the periods measured in the index [13,14]. Using such modified MPI, normal reference ranges of this parameter across gestational age have been published [15,16] showing that MPI values remain virtually unchanged between 24 to 35 weeks of gestation. Recently, evaluation of cardiac function in near term fetuses under pathological conditions is emerging [11,17,18]. Reported MPI values in gestational-age matched controls used in some of these studies [22] lie within higher values than those reported in earlier gestational ages, which suggests that MPI might increase during the last weeks of gestation. Published normal ranges include a very small number of fetuses beyond term and this raises the need to develop normative values in near-term fetuses.

The aim of this study was to construct gestational age-based reference intervals for the fetal left modified myocardial performance index in fetuses between 34 and 42 weeks of gestation.

MATERIAL AND METHODS

Subjects

Between January 2008 and December 2009, a prospective cohort of consecutive singleton fetuses was created including 30 cases for each week of gestation, between 34 to 42 weeks corrected by first trimester ultrasound [19]. Women were offered to participate at a routine third-trimester ultrasound. Only cases with an estimated fetal weight between the 10^{th} and 90^{th} percentile according to local standards [20] were included. Exclusion criteria were: congenital malformations and chromosomal abnormalities. All fetuses were followed until delivery to confirm the absence of any structural malformation by postnatal clinical examination and those cases ending up with a birthweight below the 10^{th} or above the 90^{th} percentile were not subsequently excluded. The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women (IRB 2009/4712).

Myocardial performance index

Prenatal Doppler ultrasound examinations were performed using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) ultrasound machine equipped with a 6-2 MHz linear curved-array transducer, by one of two experienced operators (D.O. or R.C.M). Using spectral Doppler, the modified MPI was measured as previously described by Hernandez-Andrade et al.[13] In brief, in a cross-sectional view of the fetal thorax, in an apical projection and at the level of the four-chamber view of the heart, the Doppler sample volume was placed to include both the lateral wall of the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves were clearly visualized (Figure 1). The images were recorded using a sample volume of 3-4mm, a gain level of 60, a Doppler sweep velocity of 8, and with the E/A waveform always displayed as positive flow. The isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) were calculated using the beginning of the mitral and aortic valves clicks as landmarks and the MPI was calculated as follows: (ICT+IRT)/ET.

All studies were performed before the onset of labor and only one set of measurements for each patient was included in the analysis.

Statistical analysis

Normal ranges were constructed by the regression model described by Royston and Wright [21]. In brief, normal distribution of MPI and its individual components was checked with the Shapiro-Francia W-test, and a natural logarithmic transformation of the data was used if necessary. Separate cubic, quadratic and linear regression models were fitted to estimate the relationship between the studied variables and gestational age (GA). Standard deviation (SD) curves as functions of GA were calculated by means of a polynomial regression procedure of absolute residuals for each measurement of interest. The 5^{th} and 95^{th} percentiles for each GA were calculated as follows: mean ± 1.645 x SD. Normal distribution of the resulting model was verified by obtaining normal probability plots of the z-scores overall and for each gestational age. A table reporting the mean and the 90% interval of prediction (5^{th} and 95^{th} percentiles) for each measurement was created.

RESULTS

During the study period a total of 245 fetuses were included. The MPI was successfully obtained in all examinations regardless of fetal position. Maternal characteristics and perinatal outcomes are summarized in Table 1. The mean gestational age at inclusion and at delivery was 37.2 and 39.8 weeks, respectively.

The best parametrical model for all the studied parameters was a first degree lineal polynomial.

Figures 2 and 3 illustrate a scatter plot with the estimated mean and percentile curves for each studied parameter across gestational age. All the studied variables showed a progressive change with advancing gestation. From 34 to 42 weeks of gestation, the mean MPI increased from 0.46 to 0.53 (MPI=exp((0.018xGA(weeks))-1.39)) with a constant SD of 0.08. Similarly, the ICT increased from 31 to 35 ms (ICT=exp ((0.015xGA(weeks)-2.92); SD=6.4ms), the IRT increased from 42 to 50ms (IRT=exp ((0.022xGA(weeks)-2.99); SD=7.7 ms) and the ET decreased from 170 to 159ms (ET=216.7- 1.37xGA(weeks); SD=12.3ms).

Table 2 shows the normal reference ranges for the MPI and its individual components including the mean and the 5^{th} and 95^{th} percentile for each gestational age.

DISCUSSION

In this study we provided normal references for fetal left modified myocardial performance index in a cohort of near term fetuses from 34 to 42 weeks of gestation and demonstrated that mean values showed a significant progressive increase with advancing gestational age, showing an increment from 0.46 at 34 weeks to 0.53 at 42 weeks.

Although previous studies evaluating the normal reference ranges across gestational age have included term fetuses, it is difficult to make comparisons with the current study because of the small numbers contained in late-gestational age groups, which could explain the variability observed in the literature. While some studies reported mean MPI values ranging from 0.35 to 0.53 that remained almost constant throughout pregnancy [14,22,23], others authors [24,25] described a gradual reduction with advancing gestational age, with mean values above 0.60, or a gradual increased across gestational age [26]. By including both the aortic and mitral valves clicks as landmarks, we previously demonstrated that this technique allows to quantify the MPI with a higher reproducibility than conventional MPI quantification, showing an inter-observer variability below 10% and a high degree of intra-observer agreement (intraclass correlation coefficient above 0.9) [13]. With such modification of MPI measurement, we and others have previously reported that MPI values slightly increase throughout pregnancy [15,16]. In these studies the reported normal ranges of this cardiovascular parameter showed values below 0.50 across all the gestational age evaluated. However, in contrast with the current study, the study population mainly included preterm fetuses and therefore, the mean MPI values in near term fetuses could had been underestimated due to a limited precision of the model at these gestational age period.

The results of this study confirm that MPI values experiment a substantial increase in late gestational ages, suggesting developmental changes in left ventricular function, especially ventricular diastolic function and myocardium maturation. In keeping with this contention, as have been demonstrated in animal models, the fetal heart experiment an increase in the number and volume of cardiac myocytes becoming hyperplasic and hypertrophic as gestation progress[27]. It could be hypothesized that the cardiac hypertrophy observed during fetal development could reduced the displacement of the heart with an increment in the isovolumetric times and reduction of the ejection time as a consequence.

In addition, although previous studies have reported slightly higher mean MPI values in term[28] than preterm[29] newborns. It is difficult to make comparisons between fetal and neonatal values due to the drastic switch from the fetal to the neonatal circulation at birth that induces changes in the cardiac output [30] and a progressive reduction of the MPI after birth[28].

The reference values here reported could be useful for cardiac function evaluation in near-term fetuses under pathological conditions such as those from diabetic mothers [11,12] and small-

for-gestational age fetuses. Milder forms of late-onset IUGR have been demonstrated to show subclinical signs of cardiac dysfunction in fetal life [17], which persist together with cardiac remodelling in childhood [18]. Clinical and investigational fetal cardiovascular evaluation is likely to expand its applications in future years. This study illustrates the importance of producing gestational adjusted values for cardiac indices in order to avoid biased results.

A strength of this study is that it includes a sensible number of cases at each gestational age, making the estimation robust throughout the entire gestational age range. Furthermore, fixed ultrasound settings were used in all examinations which allow facilitating comparability among studies. There are several considerations for the application of MPI in pregnancy. Firstly, definition of the time periods used in the MPI calculation can be challenging in advanced gestational ages due to the large size of the cardiac structures, which may render difficult recording the clicks of both mitral and aortic valves within the same waveform. In these respects, increasing the Doppler sample volume is a critical step to achieve satisfactory recordings in advanced gestational ages. MPI in this study could be examined in all cases regardless of fetal position and independently of the gestational age, but we acknowledge that recording of this index requires advanced training. As previously reported, fetal MPI estimation requires on average 65 measurements for a non-experienced examiner to achieve competence and yield reliability[31]. However, in experienced hands MPI can be measured with a low degree of variability and with a mean acquisition time of 2 minutes [13,16].

In conclusion, left myocardial performance index showed significant changes across gestational age in late third trimester fetuses. The reference values data reported in this study could be used in future studies evaluating cardiac function in term fetuses under pathological conditions.

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Table 1. Clinical characteristics of the study population (*n*=245)

Characteristic	*Mean (range) or %*
Gestational age at inclusion (weeks)	37.2 (34.0-42.0)
Maternal age (years)	30.9 (17.4-42.9)
Primiparity (%)	66.5
Non-Caucasian ethnicity (%)	18.8
Labor induction (%)	25.3
Mode of delivery	
Spontaneous vaginal (%)	61.6
Instrumental vaginal (%)	20.0
Cesarean (%)	18.4
Gestational age at delivery (weeks)	39.8 (35.4-42.1)
Birthweight (g)	3230 (2250-4200)
Birthweight centile	41.9 (5-97)
5-minute Apgar score<7 (%)	0

Table 2. Normal references values of the myocardial performance index (MPI) and its individual components (in milliseconds)

GA	MPI			ICT			IRT			ET		
	p5	p50	p95	p5	p50	p95	p5	p50	p95	p5	p50	p95
34	0,33	0,46	0,58	20,5	31,0	41,4	29,4	42,1	54,7	150	170	190
36	0,34	0,46	0,59	21,0	31,4	41,9	30,3	43,0	55,6	149	169	189
37	0,35	0,47	0,60	21,5	31,9	42,4	31,3	43,9	56,6	147	168	188
38	0,35	0,48	0,61	21,9	32,4	42,8	32,3	44,9	57,6	146	166	186
39	0,36	0,49	0,62	22,4	32,9	43,3	33,3	45,9	58,6	144	165	185
40	0,37	0,50	0,62	22,9	33,4	43,8	34,3	46,9	59,6	143	163	184
41	0,38	0,51	0,63	23,4	33,9	44,3	35,3	48,0	60,6	142	162	182
42	0,39	0,52	0,64	23,9	34,4	44,8	36,4	49,1	61,7	140	161	181

GA: gestational age; ICT: isovolumetric contraction time; IRT: isovolumetric relaxation time; ET: ejection time; p5: 5thcentile; p50; median; p95: 95thcentile.

Figure 1. Doppler image of the myocardial performance index

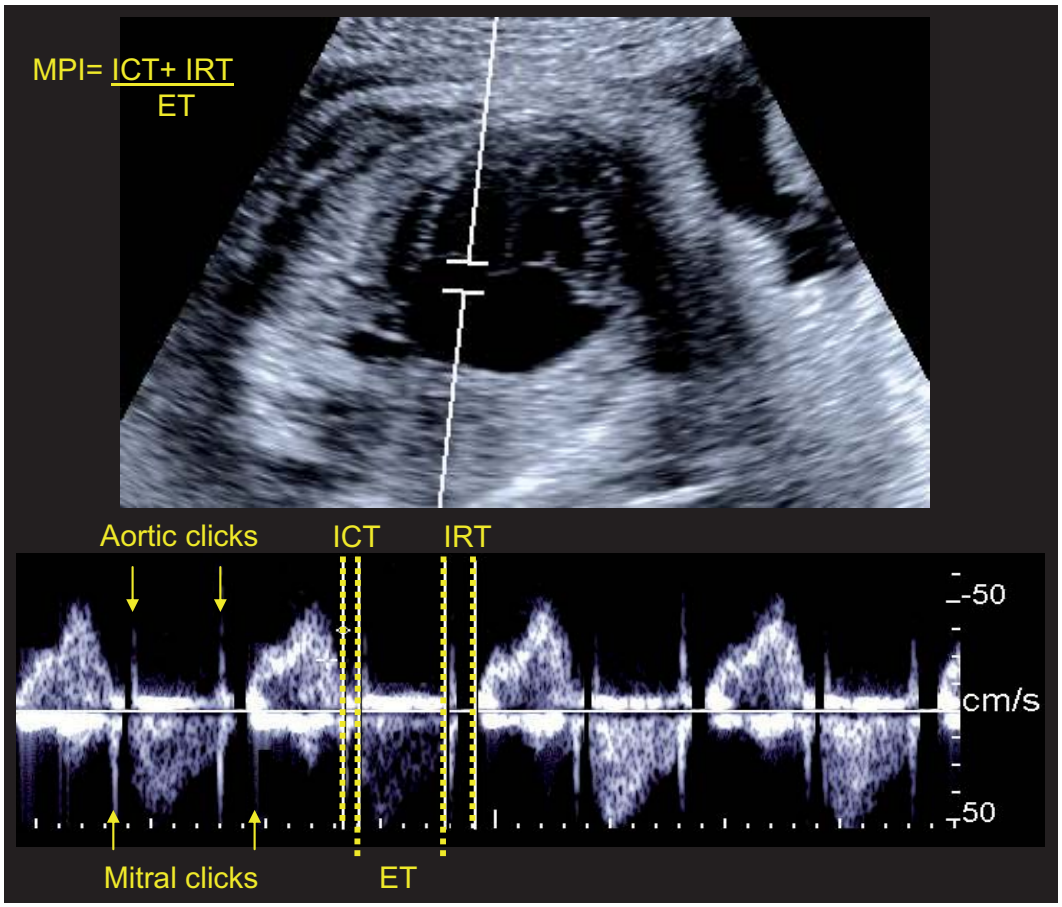


Figure 2. Plots of the myocardial performance index (MPI) against gestational age

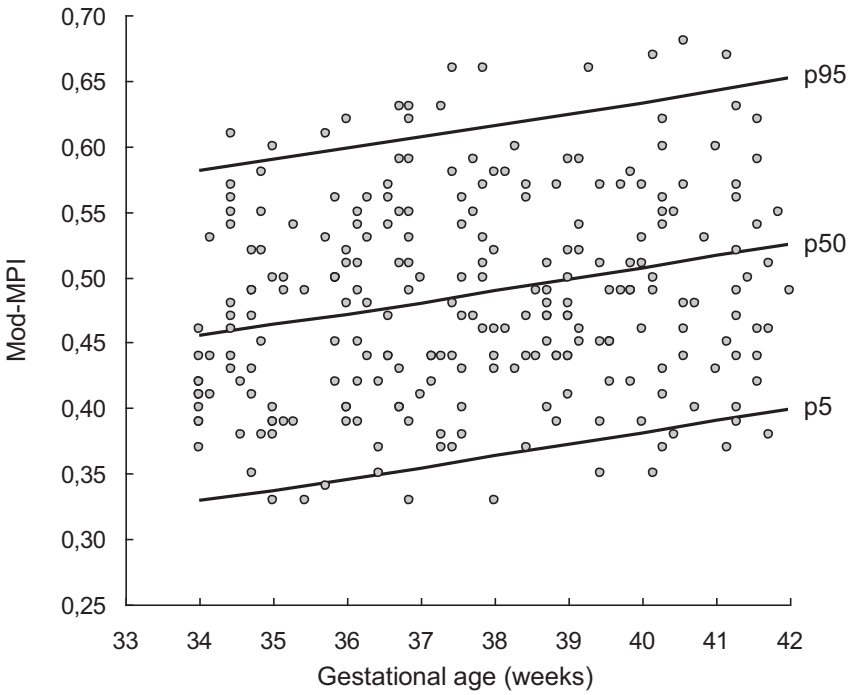
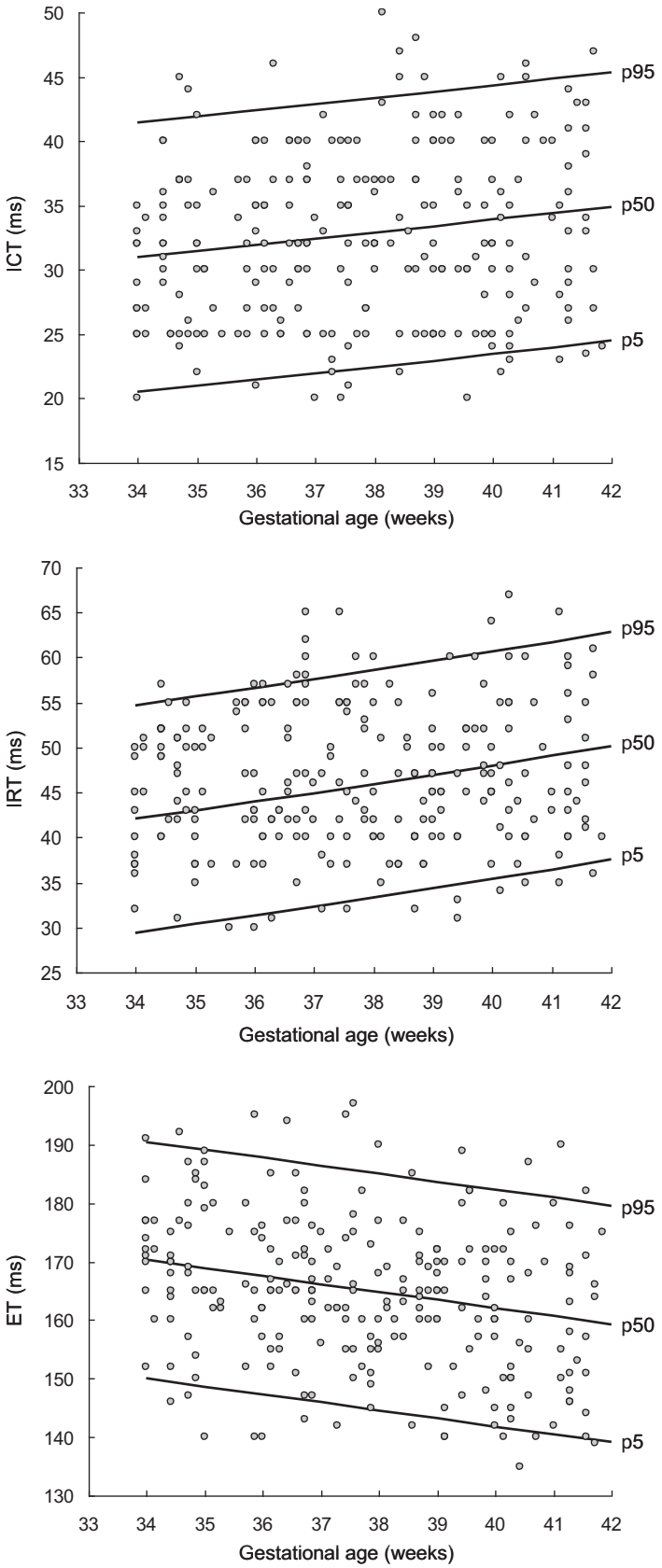


Figure 3. Plots of the isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET) against gestational age



STUDY 3

Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by Fractional Moving Blood Volume.

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OBSTETRICS

Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by fractional moving blood volume

Rogelio Cruz-Martinez, MD; Francesc Figueras, MD; Edgar Hernandez-Andrade, PhD; Bienvenido Puerto, MD; Eduard Gratacós, PhD

OBJECTIVE: The objective of this study was to compare the temporal sequence of fetal brain hemodynamic changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by fractional moving blood volume.

STUDY DESIGN: Cerebral tissue perfusion measured by fractional moving blood volume, cerebroplacental ratio, anterior cerebral artery, and middle cerebral artery pulsatility indices were weekly performed in a cohort of singleton consecutive small-for-gestational-age fetuses with normal umbilical artery delivered after 37 weeks of gestation.

RESULTS: A total of 307 scans were performed on 110 small-for-gestational-age fetuses. Mean gestational age at diagnosis and at delivery was 35.7 and 38.6 weeks, respectively. The proportion of fetuses with abnormal fractional moving blood volume, cerebroplacental ratio, anterior cerebral artery-pulsatility index, and middle cerebral artery-pulsatility index values was 31.3%, 16.8%, 17.2%, and 10.8% at 37 weeks of gestation and 42.7%, 23.6%, 20.9%, and 16.4% before delivery.

CONCLUSION: The presence of brain redistribution in small-for-gestational-age fetuses was detected earlier and in a higher proportion of fetuses using cerebral tissue perfusion rather than spectral Doppler indices.

Key words: anterior cerebral artery, cerebral blood perfusion, cerebroplacental ratio, Doppler, fractional moving blood volume, middle cerebral artery, small-for-gestational-age fetuses

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Small fetuses with normal umbilical artery (UA) Doppler are considered 1 end of the spectrum of the normal population.[1,2] However, recent evidence suggests that a substantial proportion of them have true intrauterine growth restriction (IUGR) as suggested by a poorer perinatal outcome[3-5] and an increased prevalence of abnormal neurobehavioral and neurodevelopmental tests, both neonatally[6] and in childhood.[7,8] Because identification of this subgroup of small-for-gestational-age (SGA) fetuses with true milder forms of growth restriction cannot be determined by UA Doppler, direct fetal signs, such as the assessment of brain redistribution, have been proposed.[9-12] Middle cerebral artery (MCA) pulsed Doppler has long constituted the clinical standard for the diagnosis of brain redistribution.[13] Up to 15% of term SGA have a reduced pulsatility index (PI) in the MCA, and this is associated with poorer perinatal outcome[10,11] and with an increased risk of abnormal neurobehavior at birth,[12] along with suboptimal neurodevelopmental outcome at 2 years of age.[9]

Aside from the MCA, other spectral Doppler indices reflecting brain circulation changes, such as the anterior cerebral artery (ACA) PI or the cerebroplacental ratio (CPR), have been proposed for clinical detection of brain redistribution in growth-restricted fetuses.[14-16] However, these indices have only been evaluated in groups of fetuses with early-onset IUGR, and, consequently, their behavior in SGA fetuses with normal UA PI is unknown. In contrast to indices based on the Doppler flow patterns of brain arteries, in recent years a different approach to assess fetal brain circulation has been proposed. Fractional moving blood volume (FMBV) uses power Doppler to estimate quantitatively brain tissue perfusion. This method has been validated in animal models[17] and has been demonstrated to be a reproducible[18] and potentially more sensitive method for

From the Department of Maternal-Fetal Medicine, Institut Clínic de Ginecologia, Obstetrícia i Neonatologia (ICGON); the Fetal and Perinatal Medicine Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Hospital Clinic, University of Barcelona, Barcelona, Spain (all authors).

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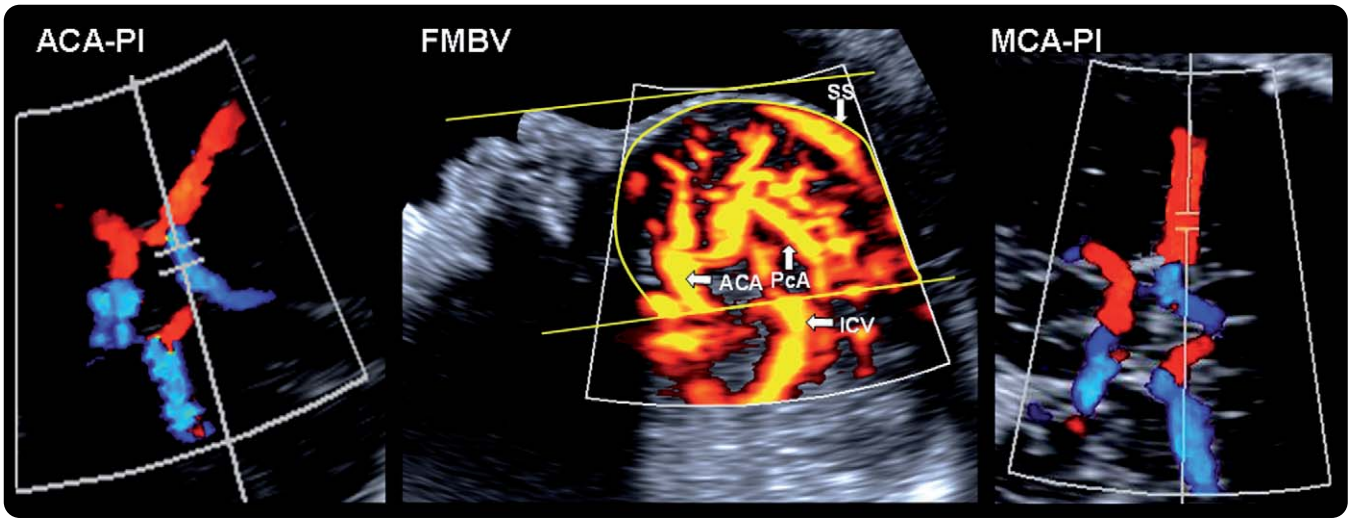
FIGURE 1
Cerebral blood perfusion's spectral and power Doppler images



ACA, anterior cerebral artery; *FMBV*, fractional moving blood volume; *ICV*, internal cerebral vein; *MCA*, middle cerebral artery; *PcA*, pericallosal artery; *PI*, pulsatility index; *SS*, sagittal sinus.

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the detection of brain blood flow redistribution in fetal growth restriction.[19] In a recent study on SGA fetuses, increased brain tissue perfusion by FMBV predicted abnormal neonatal neurobehavioral performance with better accuracy than pulsed Doppler evaluation of the MCA.[20]

Sequential evolution of previously reported brain hemodynamic parameters, based on either spectral or power Doppler, has not been evaluated in SGA near-term fetuses. This information is of clinical relevance, since parameters offering earlier detection of SGA fetuses with true forms of growth restriction might allow timely delivery in a larger number of cases. We hypothesized that evaluation of brain tissue perfusion by FMBV could be an earlier sign of brain redistribution rather than those parameters based on spectral Doppler evaluation of brain arteries. In this study, we evaluated the longitudinal changes of brain tissue perfusion measured by FMBV in relation to the changes in the MCA, CPR, and ACA Doppler indices.

Materials and Methods

Subjects

A prospective cohort was created of consecutive cases of singleton fetuses with estimated fetal weight below the 10th percentile according to local standards,[21] born beyond 37 weeks of gestation corrected by first-trimester ultrasound,[22] between December 2007–July 2009. Exclusion criteria were as follows: (1) congenital malformations and chromosomal abnormalities; (2) UA PI above the 95th percentile[23] during follow-up; and (3) confirmed birthweight above the 10th percentile according to local standards.[21] The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women. A total of 60 fetuses included in this study had been included in a previous series on SGA.[20]

Ultrasound and Doppler measurements

Prenatal Doppler ultrasound examinations were performed weekly between diagnosis and delivery by an experienced operator (R.C.M.) using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA) ultrasound machine equipped with a 6–2 MHz linear curved-array transducer. Doppler recordings were performed in the absence of fetal movements and voluntary maternal suspended breathing. Pulsed Doppler parameters were performed automatically from 3 or more consecutive waveforms, with the angle of insonation as close to 0° as possible. A high-pass wall filter of 70 Hz was used to record low blood flow velocities and avoid artifacts. UA PI was performed from a free-floating cord loop. The MCA PI was obtained in a cross-sectional view of the fetal head, at the level of its origin from the circle of Willis. The CPR was calculated as a ratio of the MCA PI divided by the UA PI. For the ACA PI, the Doppler gate was placed in its first segment, immediately after the origin of the ACA from the internal carotid artery. Normal UA was considered as a PI below the 95th percentile.[23] The MCA PI, ACA PI, or CPR values below the fifth percentile were considered indicative of cerebral blood flow redistribution.[23,24] In all cases, the last examination was performed within 1 week of delivery. Labor induction was programmed at term for cases with preeclampsia or an estimated fetal weight below the third percentile by cervical ripening. Delivery was attended by a staff obstetrician.

Cerebral blood perfusion

Using power Doppler ultrasound, frontal tissue perfusion was evaluated weekly in a sagittal view of the fetal head. In a midsagittal view of the fetal brain, the power Doppler color box was placed to include all the frontal area of the brain. Five consecutive high-quality images

TABLE
Maternal and neonatal clinical characteristics of the study group

Characteristic	SGA, n = 110
GA at inclusion, wk	35.7 (2.0)
GA at last scan, wk	37.8 (1.4)
Maternal age, y	32.0 (5.4)
Low socioeconomic class,[a] %	46.4
Primiparity, %	57.3
Nonwhite ethnicity, %	13.6
Smoking, %	26.4
1–10 cigarettes/d	18.2
10–19 cigarettes/d	1.8
≥20 cigarettes/d	6.4
Preeclampsia, %	7.3
Labor induction, %	59.1
Cesarean section, %	31.8
GA at delivery, wk	38.6 (1.3)
Birthweight, g	2394 (260)
Birthweight percentile	4.5 (3.0)
5-min Apgar score <7, %	0
Admission to the neonatal unit, %	6.4
Stay in the neonatal unit, d	1.1 (2.5)

Results are expressed as mean and standard deviation or percentage.
GA, gestational age; *SGA*, small for gestational age.
[a] Routine occupations, long-term unemployment, or never worked (UK National Statistics Socio-Economic Classification).
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with no artifacts were recorded using the following fixed US settings: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1, and pulsed repetition frequency of 610 Hz. All images were examined offline and FMBV was estimated with the MATLAB software 7.5 (The MathWorks, Natick, MA) as previously described.[25] The mean FMBV from all 5 images was considered as representative for that specific case and expressed as percentage. The region of interest (ROI) was delineated as described elsewhere:[18] anteriorly by the internal wall of the skull, inferiorly by the base of the skull, and posteriorly by an imaginary line drawn at 90° from the origin of the ACA and parallel to an imaginary line in the front of the face and crossing at the origin of the internal cerebral vein (Figure 1). Increased frontal perfusion was considered as an FMBV above the 95th percentile according to local standards.[26]

Statistical analysis

The longitudinal changes were analyzed by Kaplan-Meier survival analysis, in which the endpoint was defined as an abnormal Doppler value (MCA PI, CPR, and ACA PI below the fifth centile or FMBV above the 95th percentile). The McNemar test was used to compare qualitative data. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 15.0; SPSS, Inc, Chicago, IL) statistical software.

RESULTS

During the study period a total of 307 scans were performed on 110 SGA fetuses. UA, MCA, and ACA were successfully obtained in all examinations, whereas frontal brain perfusion could not be obtained in 4 examinations because of the degree of engagement of the fetal head into the pelvis.

The mean gestational ages at first and last scan were 35.7 (range, 29.4–38.4) and 38.6 (range, 37.0–41.9) weeks, respectively. The median interval between the last examination and delivery was 2 (range, 0–8) days. Table 1 shows the maternal and neonatal clinical characteristics of the population.

At the first scan, the proportion of cases with abnormal MCA PI, CPR, ACA PI, and FMBV was 3.6% (n = 4), 5.5% (n = 6), 2.7% (n = 3), and 9.1% (n = 10), respectively. No significant differences were observed between these proportions. At the last examination before delivery, the proportion of increased FMBV (42.7%) was significantly higher than the proportion of abnormal MCA PI (16.4%; $P < .01$), abnormal CPR (23.6%; $P < .01$), and abnormal ACA PI (20.9%; $P < .01$).

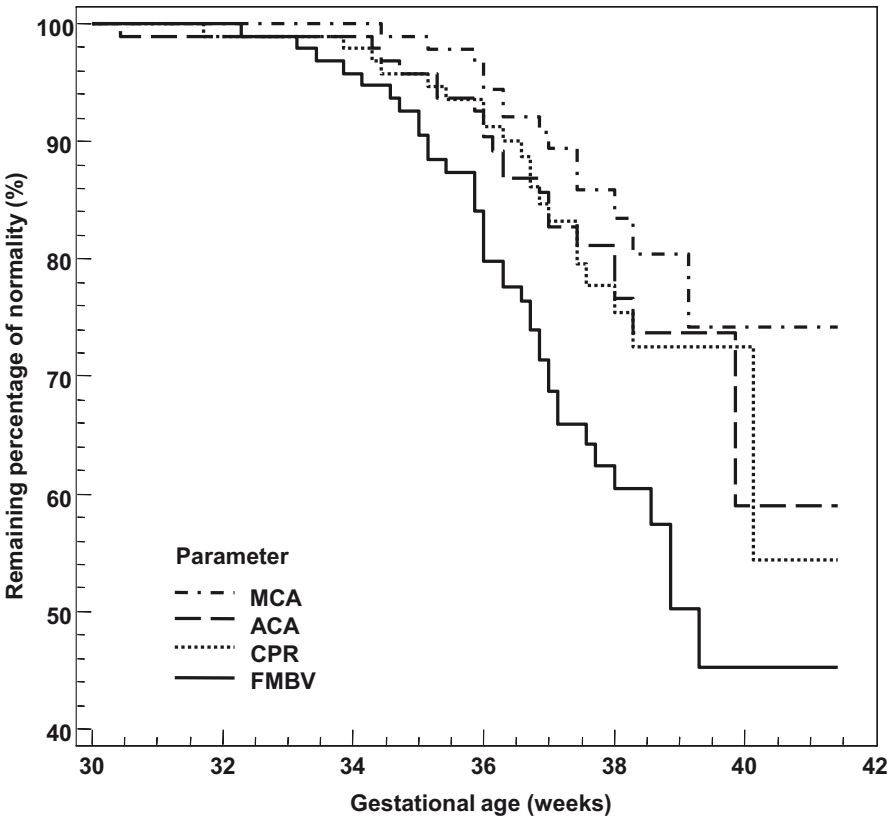
For survival analysis, cases with abnormal spectral or power Doppler at first scan were excluded, leaving a final population of 96 fetuses that were longitudinally analyzed, in whom a total of 249 scans were performed (median, 2; range, 2–5). Figure 2 shows the survival graph of the Doppler parameters throughout the study period, plotted against gestational age, which could be interpreted as the remaining proportion of normal MCA PI, ACA PI, CPR, and FMBV at each week of gestational age. At 37 weeks, the proportion of abnormal values was 10.8% (95% confidence interval [CI], 4.1–17.4) for the MCA PI, 16.8% (95% CI, 8.7–24.9) for the CPR, 17.2% (95% CI, 9.3–25.4) for the ACA PI, and 31.3% (95% CI, 21.5–41.0) for the FMBV. Similarly, the first quartile survival time (when a quarter of the population had abnormal Doppler) occurred at 39.14 weeks (95% CI, 38.1–40.2) for the MCA, at 38.3 weeks (95% CI, 37.0–39.5) for the CPR, 38.3 weeks (95% CI, 37.0–39.5) for the ACA, and 36.7 weeks (95% CI, 36.0–37.4) for the FMBV. Figure 3 depicts the changes in the proportion of abnormal Doppler between diagnosis and delivery for each parameter.

COMMENT

This study evaluated the temporal sequence of changes in brain tissue perfusion measured by FMVB in relation to other arterial spectral Doppler parameters. The study provides evidence that increased brain tissue perfusion occurs earlier and in a higher proportion of cases than CPR, MCA, or ACA pulsed Doppler abnormalities.

Intrauterine placental function evaluation by UA Doppler is today the clinical standard to distinguish between SGA and IUGR.[27-29] Although abnormal umbilical Doppler is associated with adverse perinatal and neurodevelopmental outcome,[4,5,30,31] small fetuses with normal UA Doppler have been considered constitutionally and otherwise healthy small fetuses. However, recent evidence strongly suggests that UA Doppler is not a reliable sign of placental insufficiency in mild forms of fetal growth restriction near or at term. A proportion of term SGA fetuses with normal UA PI have a higher risk of abnormal neonatal neurobehavioral performance with poorer

FIGURE 2
Cerebral Doppler parameter survival plot



ACA, anterior cerebral artery; *CPR*, cerebroplacental ratio; *FMBV*, fractional moving blood volume; *MCA*, middle cerebral artery.
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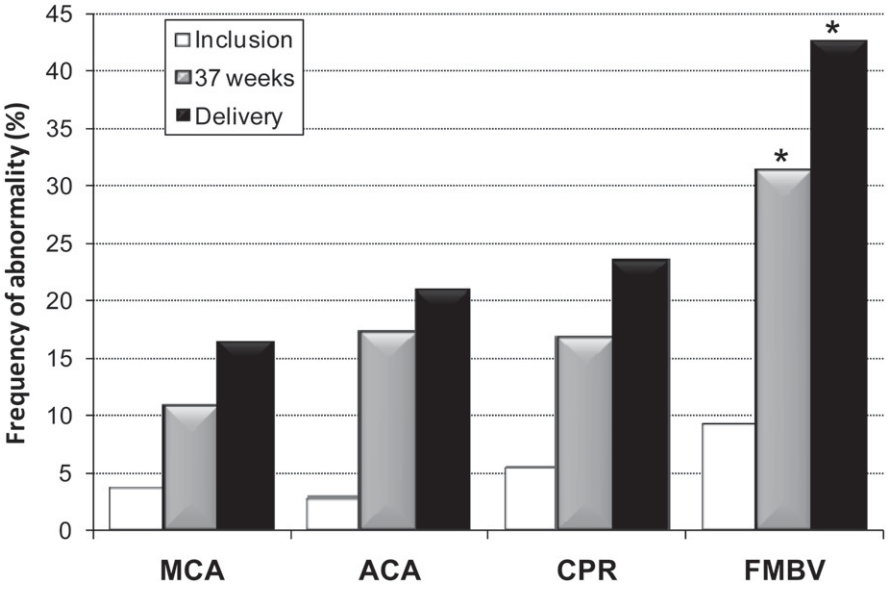
FIGURE 3
Abnormal Doppler values throughout the study period



ACA, anterior cerebral artery; *CPR*, cerebroplacental ratio; *FMBV*, fractional moving blood volume; *MCA*, middle cerebral artery. *$P < .001$.
Cruz-Martinez. Brain perfusion changes in near-term SGA fetuses. Am J Obstet Gynecol 2010.

competence to organize their state, to respond to social and nonsocial stimuli, lower attention capacity, or motor abilities.[6] Likewise, term SGA infants show a suboptimal neurodevelopmental outcome in childhood.[8] These findings suggest that in this diagnostic category there is a proportion of cases with a true form of fetal growth restriction where mild chronic hypoxia seems to have already occurred before the umbilical Doppler waveform becomes abnormal. Identification of these infants at higher risk is challenging, because early interventions may prevent subsequent behavioral disruptions.[32-34]

Chronic fetal hypoxia is consistently associated with increased brain perfusion, also defined as redistribution.[35] Consequently, brain redistribution may constitute a reliable sign to discriminate placental insufficiency in term SGA fetuses, who by definition have a normal UA. The gold standard to define brain redistribution in clinical practice is the presence of middle cerebral artery vasodilation, diagnosed by a spectral Doppler PI below the fifth percentile.[13] Several studies have demonstrated that 15–20% of SGA fetuses with normal UA Doppler have MCA vasodilation, which is associated with adverse perinatal outcome[10,11] and increased risk of abnormal neurodevelopment.[9,12] Recently, the performance of other indices reflecting brain redistribution has been investigated. The CPR combines the PI of the UA and the MCA, and it has shown to have a higher sensitivity than the UA and MCA alone to detect adverse perinatal and neurodevelopmental outcome.[36-39] However, its predictive value seems to be more powerful in preterm IUGR fetuses,[40] whereas its superiority over MCA alone is uncertain in term SGA, probably because the UA does not become altered in this diagnostic subgroup. Concerning the ACA, population-based large studies have suggested that it could be a better predictor of behavioral problems in childhood than the MCA.[41] However, in a recent study on neonates with SGA, ACA was not superior to MCA in the prediction of poor perinatal outcome.[12]

Recently, we provided evidence that estimation of brain tissue perfusion by

FMBV could be more sensitive than Doppler of the MCA to predict abnormal neonatal neurobehavior, suggesting that this parameter could be used as a means to detect a larger proportion of SGA fetuses with true hypoxia.[20] In this study, we further evaluated the longitudinal evolution of this measurement in comparison with pulsed Doppler parameters used clinically for the study of brain perfusion. The findings of this study are consistent with previous observations in fetuses with severe early-onset growth restriction, in which the onset of increased brain perfusion by FMBV occurred from earlier stages of fetal deterioration and long before a reduction in MCA PI below the fifth percentile was reached. Actually, established vasodilation of the MCA seemed to coincide with a decline in the relative perfusion of the frontal lobe in relation to other regions such as the basal ganglia.[19] Thus, a reduction in MCA PI might indicate a relatively advanced stage in the establishment of increased brain blood flow, and this may explain the reduced sensitivity of spectral Doppler of this vessel to identify early stages of increased brain perfusion in comparison to direct measurements of brain tissue perfusion as measured by FMBV.[20]

As evidence supporting an increased risk of adverse perinatal outcome and neurodevelopmental abnormalities in SGA fetuses accumulates,[3-8,10-12,42] early identification of SGA with signs of fetal hypoxia may become a critical need to allow timely delivery when term is reached. At 37 weeks, brain redistribution was twice as frequent when assessed by FMBV as by MCA pulsed Doppler. Because the former has been demonstrated to be strongly associated with adverse neurobehavioral performance,[20] this parameter seems more sensitive to detect subtle brain injury than spectral Doppler. With the diagnosis of SGA being established in about 5% of pregnancies, the benefit of increasing the detection of cases to be delivered at 37 weeks can be hardly overestimated. If our findings are confirmed in further studies, and as commercial equipments incorporate automated methods to reliably estimate blood flow perfusion, the use of FMBV or similar methods to estimate tissue perfusion might gain acceptance to detect brain redistribution in SGA and eventually replace current methods based on spectral Doppler.

One strong point of this study is that it only included a well-defined cohort of near-term SGA fetuses with normal UA Doppler. Among the limitations of the study, it must be acknowledged that, as with any Doppler method, FMBV is an indirect estimate of blood perfusion. However, the technique has shown an excellent correlation with gold standards in the estimation of true tissue blood flow in animal experiments.[17] The method has also shown good reproducibility for the assessment of fetal brain perfusion in different regions.[18] This methodology overcomes the limitations of other tools already incorporated into commercial devices to estimate blood flow, which may have substantial limitations when used in deep tissues because of an inherent lack of correction for attenuation and depth.[43,44] As mentioned previously, the clinical application of our findings is at present limited because of the unavailability of commercial US equipment with built-in methods to measure tissue brain perfusion accurately.

In conclusion, brain redistribution could be detected earlier and in a higher proportion of cases by means of FMBV, as compared with MCA or ACA pulsed Doppler indices. These findings must be confirmed but support further studies to evaluate the impact of brain tissue perfusion in monitoring of SGA fetuses. ■

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STUDY 4

Changes in myocardial performance index, aortic isthmus and ductus venosus in term, small-for-gestational age fetuses with normal umbilical artery Doppler

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Changes in myocardial performance index, aortic isthmus and ductus venosus in term, small-for-gestational age fetuses with normal umbilical artery Doppler

Rogelio Cruz-Martinez[1]; Francesc Figueras[1]; Edgar Hernandez-Andrade[1]; Daniel Oros[1]; Eduard Gratacos[1].

[1]Department of Maternal-Fetal Medicine, ICGON, Hospital Clinic-IDIBAPS, University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain.

Short Title. Cardiovascular parameters in SGA fetuses.

Correspondence to:

Francesc Figueras
Maternal-Fetal Medicine Department
Hospital Clinic, University of Barcelona
Sabino de Arana 1, 08028 Barcelona
Spain
Telephone: +34 93 227 5600,
Fax: +34 (0) 93 227 5605
e-mail: ffiguera@clinic.ub.es.

Changes in myocardial performance index, aortic isthmus and ductus venosus in term, small-for-gestational age fetuses with normal umbilical artery Doppler

ABSTRACT

Objective: To evaluate the changes in Myocardial Performance Index (MPI), Aortic Isthmus (AoI) and Ductus Venosus (DV) in term small-for-gestational age (SGA) fetuses with normal umbilical artery Doppler.

Methods: MPI, AoI and DV pulsatility indices (PI) were measured within one week of delivery in a cohort of 178 term singleton consecutive SGA fetuses with normal umbilical artery PI (<95th percentile) and 178 controls matched by gestational age. Cardiovascular parameters were converted into z-scores and defined as abnormal with values above the 95th centile.

Results: Median GA at inclusion and at delivery was 35.7 and 38.6 weeks, respectively. Compared to controls, SGA fetuses showed significantly higher values in MPI and AoI PI; and similar values in DV PI. The proportion of SGA fetuses with increased MPI was significantly higher than controls (28.1% vs. 6.7%, p<0.01). Similarly, the proportion of SGA cases with abnormal AoI was significantly higher than in controls (14.6% vs. 5.1%, p<0.01). Retrograde net blood flow in AoI was observed in 7.3% of the cases and in none of the controls.

Conclusion: A proportion of SGA fetuses show cardiovascular Doppler abnormalities. This information might be of clinical relevance in improving the detection and management of late-onset intrauterine growth restriction.

Key words: *Intrauterine growth restriction; aortic isthmus; ductus venosus; myocardial performance index; Doppler; small for gestational age.*

INTRODUCTION

Most instances of early onset intrauterine growth restriction (IUGR) are caused by placental insufficiency [1]. In such cases, placental function evaluation by umbilical artery (UA) Doppler is the clinical standard used to distinguish between small-for-gestational age (SGA) and IUGR [2-4], and those with normal UA Doppler have long been considered as constitutional small. However, recent evidence has demonstrated that this is not the case in near term growth restriction. Thus, a substantial proportion of small fetuses with normal UA Doppler have true milder forms of late-onset intrauterine growth restriction (IUGR), as demonstrated by an increased risk of adverse perinatal outcome[5], abnormal neurodevelopment[6, 7] and subclinical biochemical and ecochardiogaphic signs of cardiac dysfunction in the neonatal period [8-10] and in childhood[11]. The identification of these late-onset forms of IUGR cannot be relied on UA Doppler[12, 13], and hence recent research has focused in the investigation of further parameters which may allow identification of cases with IUGR in order to plan timely delivery and early interventions to prevent long-term consequences[14]. In these respects, most efforts have been directed to demonstrate the value of brain Doppler parameters to distinguish true IUGR from constitutional smallness[15-19]. However, little attention has been given to the evaluation of cardiovascular Doppler indices for these purposes.

Hemodynamic cardiovascular adaptation is a central feature of human growth restriction. Early-onset IUGR is associated with pronounced abnormalities in biochemical and cardiovascular Doppler parameters[9, 20] that persist into childhood[11]. Evaluation of subclinical cardiac dysfunction in early-onset IUGR is already incorporated in the management of severe IUGR by means of the ductus venosus (DV) Doppler[21]. Absent or reverse flow during the atrial contraction in this vessel is strongly associated with acidemia, myocardial necrosis and increased risk of perinatal death[22, 23]. In addition, aortic isthmus (AoI) Doppler flow has been associated with abnormal cardiac function[10, 24] and higher risk of adverse perinatal[25] and neurodevelopmental outcome[26, 27], although its integration into clinical management remains to be evaluated in future research. Finally, the myocardial performance index (MPI), which combines systolic and diastolic function, has been used to demonstrate the progression of cardiac dysfunction in early-onset IUGR, showing a correlation with biochemical markers as the severity of IUGR progresses[20, 28]. In early-onset IUGR, abnormalities in the DV, AoI and MPI appear according to a longitudinal sequence[29], which illustrates the complementary value of these indices to reflect different moments in the progression of cardiovascular fetal deterioration. We postulated that given that the diagnostic category of SGA contains a proportion of late-onset IUGR, some degree of cardiovascular abnormalities might be observed in these fetuses. The behavior of cardiovascular Doppler indices in term small fetuses with normal UA Doppler has not been investigated.

In this study we aimed at evaluating MPI, AoI and DV Doppler indices in a cohort of term, SGA fetuses with normal UA Doppler.

METHODS

Subjects

Between December 2007 and June 2010, a prospective cohort was created of consecutive cases of singleton fetuses with estimated fetal weight below the 10th percentile according to local standards [30] with normal UA pulsatility index (PI) (<95th percentile) [31] and born above 37 weeks of gestation corrected by first trimester ultrasound [32]. Exclusion criteria were: (a) congenital malformations and chromosomal abnormalities, and (b) confirmed birthweight above the 10th percentile according to local standards. Controls were defined as singleton fetuses with a birthweight between the 10th and 90th percentile for gestational age[30], selected from our general population and individually matched with cases by gestational age at inclusion (± 1 week). The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women (IRB 2009/4712).

Cardiovascular Doppler parameters

Prenatal Doppler ultrasound examinations were weekly recorded by one of two experienced operators (R.C-M. or D.O) using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) ultrasound machine equipped with a 6-2 MHz linear curved-array transducer. All spectral Doppler measurements were performed automatically from three or more consecutive waveforms, with the angle of insonation as close to 0º as possible, in the absence of fetal movements and, if required, with voluntary maternal suspended breathing. A high pass wall filter of 70 Hz was used to record low flow velocities and avoid artifacts. The mechanical and thermal indices were maintained below 1.

Umbilical artery PI was measured on a free-floating loop of the umbilical cord. The MPI was measured as previously described by Hernandez-Andrade et al.[33] In brief, in a cross-sectional view of the fetal thorax, in an apical projection and at the level of the four-chamber view of the heart, the Doppler sample volume was placed to include both the lateral wall of the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves can be clearly visualized. Spectral Doppler images were obtained using a sample volume of 3-4mm, a gain level of 60, a Doppler sweep velocity of 8, and with the E/A waveform always displayed as positive flow. The isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) were calculated using the beginning of the mitral and aortic valves clicks as landmarks and the MPI was calculated as follows: (ICT+IRT)/ET.

AoI PI was measured either in a sagittal view of the fetal thorax with clear visualization of the aortic arch, placing the gate a few millimetres beyond the origin of the left subclavian artery; or in a cross-sectional view of the fetal thorax, at level of the three vessels and trachea view, placing the gate just before the convergence of the AoI and the arterial duct [34, 35]. DV was

performed in a mid-sagittal or a transverse section of the fetal abdomen, positioning the Doppler gate at its isthmic portion.

All Doppler parameters were converted into z-scores according to published normal references and considered as abnormal with values above the 95th percentile (+1.645 z-scores) [36-38] in two consecutive observations (24-hour apart). In all cases, only the last examination within one week of delivery was included in the analysis. Labor induction by cervical ripening with prostaglandins was performed beyond 37 weeks for the cases with an estimated fetal weight below the 3rd percentile. Otherwise, induction was performed beyond 40 weeks. Delivery was attended by a staff obstetrician.

Statistical analysis

Student's t-test and Pearson Chi-squared test or exact Fisher test were used to compare quantitative and qualitative data, respectively. The Mc Nemar test was used to compare pair group proportions. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 18.0, SPSS Inc., Chicago, IL, USA) statistical software.

RESULTS

A total of 190 SGA fetuses were included from whom 12 were excluded for a birthweight above the 10th centile, leaving a population of 178 consecutive SGA cases matched with 178 controls, resulting in a final population of 356 fetuses. All the studied cardiovascular Doppler parameters were successfully performed in all cases.

Table 1 shows the maternal and neonatal clinical characteristics of the population. According to our matched design, gestational age at inclusion was similar between cases and controls, but gestational age at delivery was significantly lower in the SGA group. Labor induction and cesarean section were significantly more frequent in the SGA group.

Table 2 depicts the differences in the three cardiovascular Doppler parameters between the study groups. While no differences were observed in DV PI, SGA fetuses showed significantly higher mean MPI values (0.56 vs. 0.49; t=6.8; p<0.01) and AoI PI (3.84 vs. 2.87; t=3.6; p<0.01) than controls.

Figure 1 shows the proportion of cases with abnormal Doppler parameters (above the 95th percentile) by study groups. The rate of cases with abnormal DV PI was similar between cases and controls. However, SGA fetuses had more frequently abnormal MPI values (28.1% vs. 6.7%; χ^2=28.2, p<0.01). Similarly, the proportion of fetuses with abnormal AoI PI was 14.6% in the SGA group and 5.1% in controls (χ^2=9.1, p<0.01). AoI retrograde net blood flow was observed in 7.3% of the SGA fetuses and in none of the controls (Fisher's exact test p<0.01). Of

note, the proportion of abnormal MPI was significantly higher than the proportion of abnormal AoI PI (28.1% vs. 14.6%; Mc Nemar $p<0.01$).

DISCUSSION

This study provides further evidence that a proportion of term SGA fetuses with normal UA Doppler show Doppler signs of cardiovascular adaptation/dysfunction in the form of an increased myocardial performance index and aortic isthmus impedance. This notion had been suggested by previous studies. Girsen et al[9, 10] evaluated cardiac function by Doppler and cord blood biomarkers in IUGR fetuses with different degrees of severity. The authors described that the small group of SGA fetuses with normal UA Doppler evaluated in their studies had significant differences in cardiac function parameters, which included the MPI and levels of erythropoietin and N-terminal peptide of proB-type natriuretic peptide. In line with these findings, Chaiworapongsa et al.[8] reported detectable levels of cardiac troponin I in 4.2% of 72 SGA neonates, indicating the existence of myocardial injury in this subgroup. Finally, Crispi et al.[11] recently published that SGA fetuses with normal UA Doppler have cardiac remodeling and echocardiographic subclinical signs of cardiac dysfunction in childhood as compared with normally grown children born at the same gestational age.

This study adds to previous knowledge by evaluating a large group of term, SGA fetuses and first describing the pattern of changes in MPI, AoI and DV. Elevation in MPI was the most frequent abnormality with 28% of SGA fetuses showing abnormal values (Figure 2a). These findings are in line with previous studies in early-onset IUGR fetuses, where MPI shows a correlation with the hemodynamic deterioration and with the progressively increased levels of cardiac dysfunction biomarkers[9, 20]. In early-onset IUGR MPI becomes abnormally elevated from early stages of fetal deterioration in relation to changes in AoI PI and DV PI, which occur later [29]. Thus, increased MPI values are found in virtually all early-onset IUGR fetuses from the time of diagnosis, and on average they occur 2 and 3 weeks earlier than AoI and DV changes respectively, suggesting that MPI is highly sensitive to subtle forms of fetal hypoxia. Such high sensitivity, which constitutes a limitation for its clinical use to predict fetal death in early-onset IUGR[39], might turn an advantage in SGA, since MPI could be used as a marker of fetal hypoxia, and thus of late-onset IUGR. The results of this study deserve further evaluation to assess the value of MPI to predict poor perinatal outcome, as previously demonstrated for brain Dopplers[15-19], among SGA fetuses.

Concerning the aortic isthmus, 15% of SGA with normal UA PI showed AoI abnormalities. Interestingly, 50% of these had reversed diastolic flow (Figure 2b), which is normally regarded as a sign of advanced hypoxia[24]. Several studies in animal models and human fetuses with severe placental insufficiency have found that retrograde net blood flow in the aortic isthmus is associated with increased levels of cardiac dysfunction biomarkers[10, 40]. While previous studies have reported the presence of this sign in association with positive diastolic flow in the umbilical artery[41, 42], to our knowledge this study first demonstrates that AoI retrograde net blood flow may be observed in the presence of normal UA impedance. This observation further illustrates the

poor performance of umbilical artery Doppler as a marker of risk in near term late-onset IUGR. In early-onset IUGR, recent evidence supports the clinical use of AoI for improving the prediction of adverse perinatal outcome and abnormal neurodevelopment[43]. The results of this study support further research to explore the predictive value of abnormal AoI values in late-onset IUGR.

The proportion of cases with increased DV PI was similar to that of controls. This finding could be expected in view of the evolution of DV PI in early-onset IUGR. In such cases, abnormal DV values are a late onset finding which indicates an advanced stage in the progression of fetal hypoxia[44, 45], and hence its high predictive value for perinatal death[22, 23]. The findings of this study confirm the otherwise expected notion that DV Doppler provides no information in the management of late-onset IUGR.

The results of this study add to the body of evidence supporting that a proportion of term SGA fetuses are in reality late-onset IUGR with mild forms of placental insufficiency. The findings further support future studies exploring the role of cardiovascular parameters in combination with brain Doppler parameters to improve the prediction of adverse perinatal outcome, abnormal neurodevelopment and postnatal cardiac dysfunction. As evidence suggesting intrauterine growth restriction as a potential risk factor of abnormal neurodevelopment and cardiovascular disease accumulates[6, 7, 11, 46, 47], early identification of late-onset IUGR may become a critical need for planning fetal surveillance, timely delivery and post-natal follow up. In addition, future research on cardiovascular changes in mild forms of IUGR might help to improve the understanding of fetal programming of postnatal cardiac disease[48].

Strengths of this study are that it included a well-defined cohort of term SGA fetuses with normal UA PI, all Doppler parameters were performed within one week of delivery and all abnormal values were confirmed in at least two consecutive examinations. Among the limitations of the study, it could be acknowledged that in advanced gestational age identification of the four valve clicks required for MPI calculation is technically difficult and it requires training to achieve competence. However, as we demonstrated in previous studies, even in inexperienced hands MPI measurement yielded reliability after a substantial number of examinations[49] and could be performed with a low degree of disagreement between experienced examiners using fixed specific settings and the aortic and mitral valve clicks as landmarks[33]. Similarly, recent studies have suggested that the feasibility of aortic isthmus may be limited due to the challenges posed by proper positioning of Doppler sample volume in the longitudinal view of the aortic arch[50]. However, as we and others previously reported, its evaluation at level of the three vessels and trachea view substantially improves feasibility[34, 35]. In this study AoI evaluation was possible in all cases regardless of fetal position.

In summary, our study demonstrates the existence of cardiovascular Doppler abnormalities in term SGA fetuses. Further research is required to assess whether these changes could be used to distinguish SGA fetuses with true hypoxia from constitutional smallness and to improve clinical management of late-onset IUGR.

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Table 1. Maternal and neonatal clinical characteristics of the study group. Results are expressed as mean and standard deviation or percentage.

	AGA, *n* = 178	**SGA**, *n* = 178	*p***
GA at ultrasound (weeks)	38.1 (1.3)	38.2 (1.3)	0.66
Maternal age (years)	31.8 (5.5)	31.2 (5.1)	0.35
Low socio-economic class* (%)	35.4	44.4	0.08
Primiparity (%)	61.2	54.5	0.19
Non-Caucasian ethnicity (%)	27.0	21.3	0.22
Smoking (%)	18.0	25.8	0.07
Labor induction (%)	27.0	83.1	<0.01
Cesarean section (%)	18.5	34.8	<0.01
GA at delivery (weeks)	39.8 (1.3)	38.5 (1.2)	<0.01
Birthweight (g)	3196 (377)	2376 (285)	<0.01
Birthweight centile	39.0 (23.5)	3.89 (3.5)	<0.01

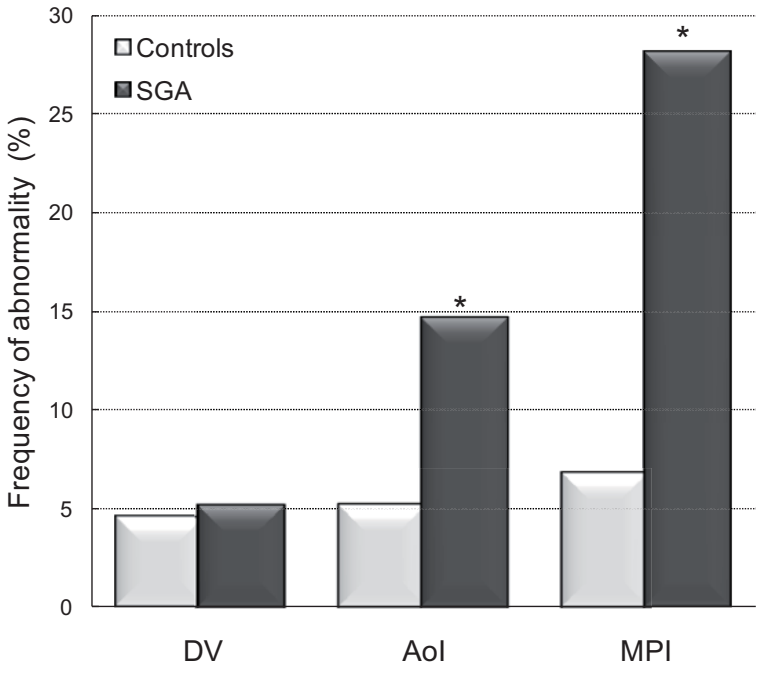
AGA: adequate-for-gestational-age; SGA: small-for-gestational-age; GA: gestational age; **Student's t-test for independent samples or Pearson-χ^2 test. * Routine occupations, long-term unemployment or never worked (UK National Statistics Socio-Economic Classification).

Table 2. Maternal and neonatal clinical characteristics of the study group. Results are expressed as mean and standard deviation or percentage.

	AGA, *n* = 178	**SGA**, *n* = 178	*p**
Myocardial performance index (z-scores)	-0.389	0.929	<0.01
Aortic isthmus PI (z-scores)	0.054	1.221	0.01
Ductus venosus PI (z-scores)	0.036	0.238	0.07

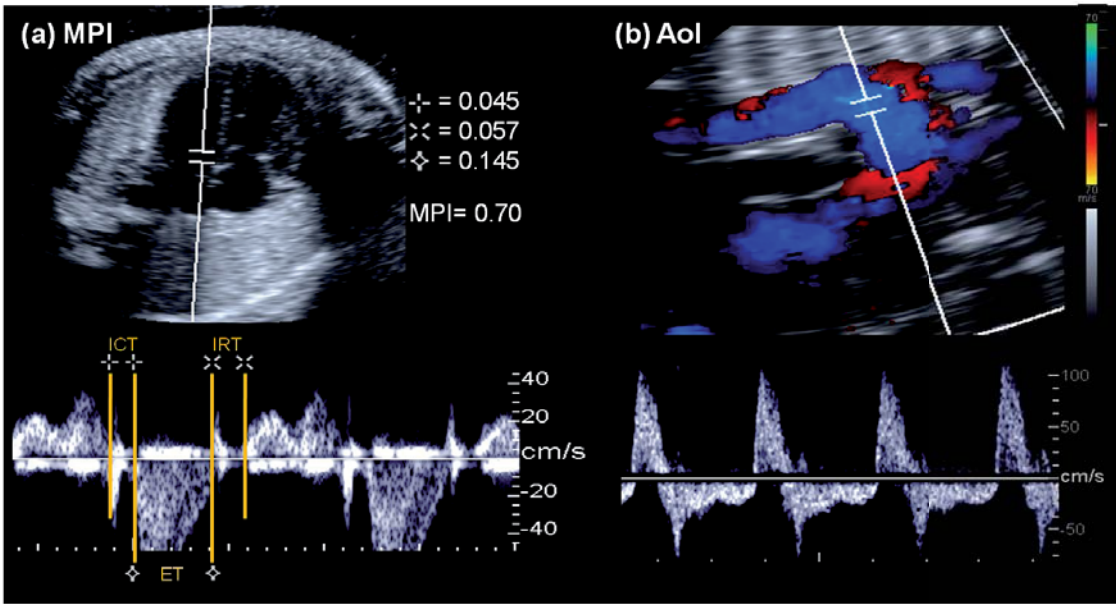
AGA: adequate-for-gestational-age; SGA: small-for-gestational-age; PI: Pulsatility Index; *Student's t-test for independent samples

Figure 1. Abnormal Doppler values between the study groups.



MPI: Myocardial Performance Index; DV: Ductus Venosus; AoI: Aortic Isthmus; *p<0.01.

Figure 2. Illustrative echographic picture of a term SGA case with increased Myocardial Performance Index (MPI) and reversed diastolic flow in the Aortic Isthmus (AoI).



STUDY 5

Fetal brain Doppler to predict cesarean delivery for non-reassuring fetal status in term, small-for-gestational age fetuses

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Fetal Brain Doppler to Predict Cesarean Delivery for Nonreassuring Fetal Status in Term Small-for-Gestational-Age Fetuses

Rogelio Cruz-Martínez, MD, Francesc Figueras, MD, PhD, Edgar Hernandez-Andrade, MD, PhD, Daniel Oros, MD, and Eduard Gratacos, MD, PhD

OBJECTIVE: To estimate the value of fetal brain Doppler in predicting the risk of cesarean delivery for nonreassuring fetal status and neonatal acidosis after labor induction in small-for-gestational-age fetuses with normal umbilical artery Doppler.

METHODS: Fetal brain Doppler parameters, including cerebral tissue perfusion measured by fractional moving blood volume, cerebroplacental ratio, and middle cerebral artery pulsatility index, were evaluated before labor induction in a cohort of 210 term small-for-gestational-age fetuses with normal umbilical artery Doppler and 210 control participants matched by gestational age. The value of the cerebral Doppler indices to predict the risk of cesarean delivery, cesarean delivery for nonreassuring fetal status, and neonatal acidosis was analyzed.

RESULTS: Overall, small-for-gestational-age fetuses showed a significant higher incidence of cesarean delivery (37.6% compared with 19.5%, $P<.001$), cesarean delivery for nonreassuring fetal status (29% compared with 4.8%, $P<.001$), and neonatal acidosis (7.6% compared with 2.4%, $P=.03$) than control participants. Within the small-for-gestational-age group, middle cerebral artery vasodilation was associated with the highest risk of cesarean delivery (67.7% compared with 32.4%, $P<.001$) and cesarean delivery for nonreassuring fetal status (58.1% compared with 24%, $P<.001$). In the subgroup of normal middle cerebral artery, incorporation of cerebroplacental ratio further distinguished two groups with different risks of cesarean delivery (51.4% compared with 27.5%, $P<.01$) and cesarean delivery for nonreassuring fetal status (37.8% compared with 20.4%, $P=.01$). Middle cerebral artery vasodilation was associated with increased risk of neonatal acidosis (odds ratio, 9.0). Fractional moving blood volume was not associated with the risk of cesarean delivery for nonreassuring fetal status or neonatal acidosis.

CONCLUSION: Evaluation of brain Doppler indices before labor induction discriminates small-for-gestational-age fetuses at high risk of cesarean delivery for nonreassuring fetal status and neonatal acidosis.

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LEVEL OF EVIDENCE: II

Small-for-gestational age fetuses without signs of placental insufficiency as reflected in the umbilical artery Doppler account for up to 10% of the pregnant population by customized centiles.[1] Recent evidence suggests that a proportion of these small-for-gestational-age fetuses have milder forms of late-onset intrauterine growth restriction (IUGR) as suggested by an increased risk of adverse perinatal outcome,[2–4] abnormal neonatal neurobehavioral performance,[5] and suboptimal neurodevelopment in childhood.[6,7] Thus, the identification of small-for-gestational-age fetuses with late-onset

From the Department of Maternal-Fetal Medicine, Institute Clínic of Gynecology, Obstetrics and Neonatology (ICGON), Hospital Clinic-IDIBAPS, University of Barcelona and the Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain.

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Corresponding author: Eduard Gratacos, PhD, Maternal-Fetal Medicine Department, Hospital Clinic, University of Barcelona, Sabino de Arana 1, 08028 Barcelona, Spain; e-mail: gratacos@clinic.ub.es.

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IUGR is challenging and cannot only be based on umbilical artery Doppler.

Recent studies suggest that the risk of adverse outcome in these fetuses is best established by means of brain Doppler examination. Thus, brain sparing as measured by the middle cerebral artery Doppler is associated with poorer perinatal outcome,[8] higher risk of cesarean delivery for nonreassuring fetal status,[9] and increased risk of abnormal neurodevelopmental tests at birth[10] and at 2 years of age.[11] The combination of middle cerebral artery and umbilical artery Doppler in the cerebroplacental ratio further improves the prediction of adverse perinatal outcome.[12–15] In addition, brain tissue perfusion measured by power Doppler and estimated by fractional moving blood volume, as a quantitative methodology to estimate blood tissue perfusion, has been demonstrated to be more sensitive than middle cerebral artery and cerebroplacental ratio for early detection of brain redistribution in term small-for-gestational-age fetuses[16] and to identify those cases at risk of abnormal neurobehavior.[17]

Small-for-gestational-age fetuses are often managed by induction of labor.[18–20] However, clinical studies have reported an increased risk of cesarean delivery for nonreassuring fetal status in these fetuses.[9] Predicting this risk might allow timely delivery, assist the decision-making process regarding labor induction, and result in a more efficient provision of resources at delivery. The aim of this study was to estimate whether a combination of middle cerebral artery Doppler, cerebroplacental ratio, and brain perfusion by fractional moving blood volume could improve the prediction of cesarean delivery for nonreassuring fetal status and neonatal acidosis after labor induction in term small-for-gestational-age fetuses with normal umbilical artery Doppler.

MATERIALS AND METHODS

Between January 2008 and May 2010, a prospective cohort of consecutive singleton fetuses with an estimated fetal weight below 10th percentile according to local standards,[21] normal umbilical artery Doppler (pulsatility index below the 95th percentile),[22] and cephalic presentation was selected for labor induction beyond 37 weeks of gestation corrected by first-trimester ultrasound.[23] Sample size was estimated according to the formula described elsewhere.[24] Exclusion criteria were: 1) congenital malformations and chromosomal abnormalities; and 2) confirmed birth weight above the 10th percentile according to local standards.[21] Control participants were selected during the same study period and were defined as singleton pregnancies with labor induction for premature rupture of membranes without clinical suspicion of chorioamnionitis and resulting in a neonatal birth weight between the 10th and 90th percentiles.[21] Control participants were individually matched with cases by gestational age at delivery (±1 week). The protocol was approved by the hospital ethics committee and written consent was obtained for the study from all the women involved (Institutional Review Board 2008/4422).

Prenatal Doppler ultrasound examinations were weekly performed by one experienced operator (R.C.M.) using a Siemens Sonoline Antares ultrasound machine equipped with a 6-2-MHz linear curved-array transducer. Doppler recordings were performed in the absence of fetal movements and voluntary maternal suspended breathing. Spectral Doppler parameters were performed automatically from three or more consecutive waveforms with the angle of insonation as close to zero as possible. A high-pass wall filter of 70 Hz was used to record low flow velocities and avoid artifacts. Umbilical artery pulsatility index was performed from a free-floating cord loop. The middle cerebral artery pulsatility index was obtained in a transversal view of the fetal head, at the level of its origin from the circle of Willis, and the cerebroplacental ratio was calculated as a ratio of the middle cerebral artery pulsatility index to the umbilical artery pulsatility index. Using power Doppler ultrasound, fractional moving blood volume was estimated as previously described.[25] Briefly, in a sagittal view of the fetal head, the color box was placed to include the whole frontal lobe and thus the anterior cerebral artery, pericallosal artery, median callosal artery, sagittal sinus, and the frontal medial branches. Five consecutive high-quality images with no artifacts were recorded using the following fixed ultrasound setting: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1, and pulsed repetition frequency of 610 Hz. All images were examined offline and the region of interest was delineated anteriorly by the internal wall of the frontal bone, inferiorly by the base of the skull, and posteriorly by an imaginary line drawn at 90° at the level of the origin of the anterior cerebral artery and crossing at the level of the origin of the internal cerebral vein (Fig. 1). The mean fractional moving blood volume values from all five images was considered as representative for that specific case and expressed as a percentage.

The middle cerebral artery pulsatility index and cerebroplacental ratio values below the fifth percentile and increased fractional moving blood volume

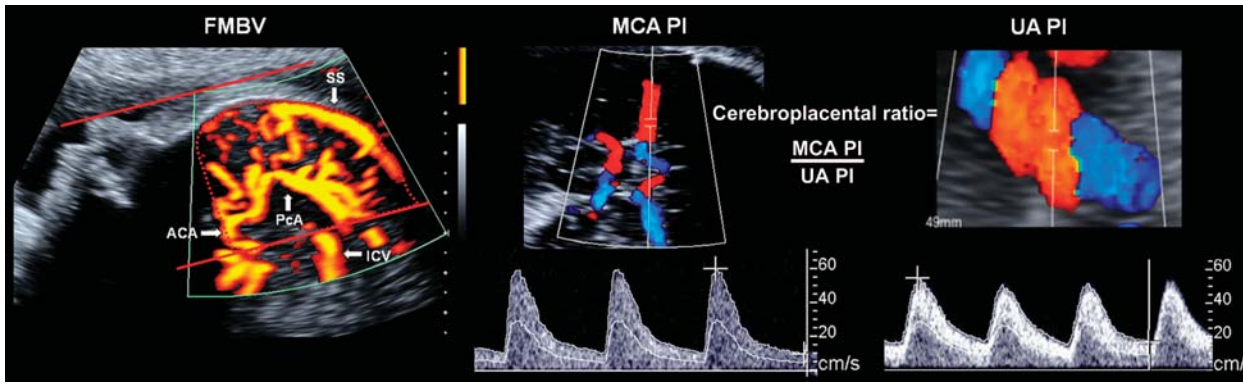

Fig. 1. Spectral and power Doppler parameters. FMBV, fractional moving blood volume; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; SS, sagittal sinus; PcA, pericallosal artery; ACA, anterior cerebral artery; ICV, internal cerebral vein.

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above the 95th percentile were considered indicative of cerebral blood flow redistribution.[26,27] Doppler indices with confirmed abnormal values at least 24 hours apart were considered as abnormal. In all cases, only the last examination within 24 hours before the onset of labor induction was included in the analysis.

Labor induction was performed at term (37 weeks or greater) for all small-for-gestational-age cases by cervical ripening with a slow-release prostaglandin estradiol vaginal pessary (10 mg). If the onset of labor did not occur within 12 hours, oxytocin induction was performed. All deliveries were attended by a staff obstetrician blinded to the results of the brain Doppler parameters evaluated in this study. Indication of cesarean delivery for nonreassuring fetal status was based on abnormal fetal heart rate tracing[28] and abnormal fetal scalp blood pH during intrapartum monitoring. Briefly, continuous fetal heart rate monitoring was performed and tracings were classified as normal, suspicious, or abnormal according to the presence, type, and length of decelerations; bradycardia; tachycardia; and the assessment of variability.[28] In cases with two or more criteria of suspicion and one or more criteria of abnormality not responding to fetal scalp digital stimulation, a fetal scalp blood sampling was attempted and considered as abnormal with values below 7.2.

Cases in which cervical conditions did not allow fetal scalp sampling were considered for cesarean delivery for nonreassuring fetal status if abnormal tracing persisted after pessary withdrawal and 10 minutes of intravenous infusion of ritodrine (200 μg/min). Metabolic acidosis was defined as the presence of an umbilical artery pH below 7.15 and base excess greater than 12 mEq/L in the newborn.[29] All cases with adverse outcome are evaluated in a confidential enquiry to assure adherence to such guidelines.

Student's t test or paired Student's t and McNemar tests were used to compare independent and paired data, respectively. The association between abnormalities in the brain Doppler parameters and the risk of emergency cesarean delivery for nonreassuring fetal status and metabolic acidosis was analyzed by multiple simple logistic regression (for independent data) or conditional logistic regression (for paired data) adjusted by estimated fetal weight percentile and gestational age at birth using Statistical Package for the Social Sciences 17.0 statistical software.

A predictive model for the occurrence of intrapartum cesarean delivery and emergency cesarean delivery for nonreassuring fetal status was constructed using the Decision Tree Analysis algorithm (SPSS 17.0), which provides clinically comprehensive classification algorithms that allow their use in clinical practice to profile the individual risk for a given patient. The decision tree was developed using the Classification and Regression Trees CHAID method (Quick, Unbiased and Efficient Statistical Tree), which generates binary decision trees with the P inset at .05 (Bonferroni-adjusted for multiple comparisons) and a cutoff selected automatically for all the parameters included.[30] The classification and regression tree was constructed by splitting subsets of the data set using all predictor variables to create two child nodes repeatedly. The best predictor was chosen using a variety of impurity and diversity measures. For a parsimonious model, the number of cases to be present for a split has to be greater than 5% of the sample. Thus, the stopping rules for the iterative process were that the tree should have a maximum of

three levels, a minimum of 10 cases were to be present for a split to be calculated, and any given split should not generate a group with less than five cases. This allowed sequential analysis of variables to predict the risk of intrapartum cesarean delivery.

RESULTS

During the study period, a total of 232 consecutive small-for-gestational-age fetuses with estimated fetal weight less than the 10th percentile fulfilling the inclusion criteria were recruited. One neonate was excluded because a nondiagnosed congenital malformation and eight additional cases because of a normal birth weight, leaving a total population of 223 cases.

In 13 cases (5.8%), frontal brain perfusion could not be evaluated as a result of the degree of engagement of the fetal head into the pelvis, leaving 210 cases for the analysis that were matched with 210 control participants, resulting in a final population of 420 fetuses.

Table 1 shows the maternal and neonatal clinical characteristics of the population. According to our matched design, gestational age at inclusion and at delivery was similar between cases and control participants. Small-for-gestational-age fetuses showed a significantly higher rate of cesarean delivery, emergency cesarean delivery resulting from nonreassuring fetal status, and neonatal acidosis than control participants. In 64% of the small-for-gestational age group with nonreassuring fetal status (in 39 of 61), the diagnosis was made during the latent phase (in 18 of 39 fetal scalp samplings was not performed as a result of the unfavorable cervical conditions) and in 36% during the first or second stages of labor. The proportion of small-for-gestational-age fetuses with increased fractional moving blood volume, abnormal cerebroplacental ratio, and middle cerebral artery vasodilation was 42.4%, 28.6%, and 14.8%, respectively.

Table 1. Maternal and Neonatal Clinical Characteristics of the Study Group*

	Control Participants (n=210)	SGA (n=210)	P†
Gestational age at inclusion (wk)	38.4±1.2	38.3±1.2	.37
Maternal age (y)	30.9±5.3	31.6±5.4	.18
Primiparity	55.2	53.8	.85
Nonwhite ethnicity	20.5	17.1	.45
Preeclampsia	3.29	6.19	.50
Cesarean delivery	19.5	37.6	<.001
Cesarean delivery for fetal distress	4.76	29.0	<.001
Gestational age at birth (wk)	38.7±1.2	38.6±1.2	.56
Birth weight (g)	3,175±394	2,385±279	<.001
Birth weight centile	43.6±25.8	3.66±3.01	<.001
5-min Apgar score less than 7	0	0	NA
Neonatal acidosis	2.38	7.62	.03

SGA, small for gestational age.
Data are mean±standard deviation or % unless otherwise specified.
* Results are expressed as mean and standard deviation or percentage.
† Student's *t* and paired *t* test for independent and paired samples or McNemar test.

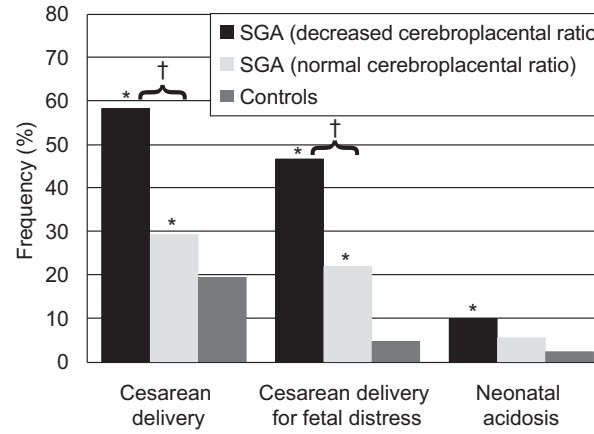

Fig. 2. Frequency of intrapartum cesarean delivery, emergency cesarean for nonreassuring fetal status, and neonatal acidosis in controls and small-for-gestational age (SGA) fetuses with and without decreased cerebroplacental ratio. *$P<.05$ with control participants the reference group; †$P<.01$ among SGA cases.

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Figures 2 and 3 show the frequency of intrapartum cesarean delivery, cesarean delivery resulting from nonreassuring fetal status, and neonatal acidosis for control participants and for small-for-gestational-age fetuses classified according to the presence or absence of decreased cerebroplacental ratio or middle cerebral artery vasodilation. Within the group of small-for-gestational-age fetuses, those fetuses with middle cerebral artery vasodilation had a significantly higher incidence of intrapartum cesarean delivery (67.7% compared with 32.4%, $P<.001$), cesarean delivery for nonreassuring fetal status (58.1% compared with 24.0%, $P<.001$), and neonatal acidosis (19.4% compared with 5.6%, $P=.01$) than those with normal middle cerebral artery Doppler. Small-for-gestational-age fetuses with abnormal cerebroplacental ratio had a significantly higher incidence of intrapartum cesarean delivery (58.3% compared with 29.3%, respectively, $P<.01$) and a higher rate of cesarean delivery for nonreassuring fetal status (46.7% compared with

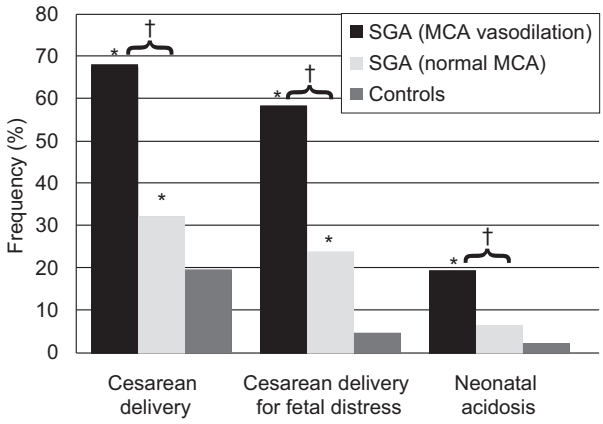

Fig. 3. Frequency of intrapartum cesarean delivery, emergency cesarean for nonreassuring fetal status, and neonatal acidosis in control participants and small-for-gestational age (SGA) fetuses with and without middle cerebral artery (MCA) vasodilation. *$P \leq .01$ with control participants as the reference group; †$P \leq .01$, among SGA cases.

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22.0%, respectively, $P<.01$) than those small-for-gestational-age cases with normal cerebroplacental ratio. Abnormal cerebroplacental ratio was not significantly associated with the risk of neonatal acidosis (10.0% compared with 6.7%, respectively, $P=.50$). Small-for-gestational-age fetuses with increased or normal fractional moving blood volume had similar risks of intrapartum cesarean delivery (41.6% compared with 34.7%, respectively, $P=.22$), emergency cesarean delivery for nonreassuring fetal status (33.7% compared with 25.6%, respectively, $P=.14$), or neonatal acidosis (9.0% compared with 6.6%, respectively, $P=.50$).

Detection and false-positive rates of middle cerebral artery for cesarean delivery for nonreassuring fetal status were 29.5% and 8.7%, whereas they were 45.9% and 21.5% for cerebroplacental ratio. For neonatal acidosis, the detection rate was 37.5% (false-positive of 12.9%) for middle cerebral artery and 37.5% (false-positive of 27.8%) for cerebroplacental ratio.

Table 2 shows the odds ratios of emergency cesarean delivery for nonreassuring fetal status and neonatal acidosis according to each brain Doppler parameter with control participants as the reference group.

The decision tree analysis (Fig. 4) profiled three groups with increasing risk of intrapartum cesarean delivery and cesarean delivery secondary to nonreassuring fetal status. Middle cerebral artery pulsatility index was the best initial predictor discriminating a group with the highest risk of CD (67.7% in small-for-

Table 2. Odds Ratios and Their 95% Confidence Intervals for Cesarean Delivery for Nonreassuring Fetal Status and Neonatal Acidosis According to Brain Doppler Referenced Against the Control Group

	CD for Nonreassuring Fetal Status		Neonatal Acidosis	
	OR	95% CI	OR	95% CI
MCA vasodilation	18.0	2.84–750	9.0	1.25–395
Decreased CPR	10.3	3.22–52.8	5.0	1.06–46.9
Increased FMBV	7.5	2.64–29.3	4.0	0.79–38.7
Normal MCA	5.1	2.37–12.7	2.0	0.62–7.46
Normal CPR	5.6	2.13–18.6	2.0	0.43–12.4
Normal FMBV	7.3	2.55–28.4	2.7	0.63–15.6

CD, cesarean delivery; OR, odds ratio; CI, confidence interval; MCA, middle cerebral artery; CPR, cerebroplacental ratio; FMBV, fractional moving blood volume.

gestational-age fetuses with middle cerebral artery vasodilation compared with 32.4% in those with normal middle cerebral artery, $P<.001$) and cesarean delivery for nonreassuring fetal status (58.1% compared with 24%, respectively, $P<.001$). In the subgroup of normal middle cerebral artery, incorporation of cerebroplacental ratio identified two groups with different risk of cesarean delivery (51.4% in small-for-gestational-age fetuses with decreased cerebroplacental ratio compared with 27.5% in those with normal cerebroplacental ratio, $P<.01$) and cesarean delivery for nonreassuring fetal status (37.8% compared with 20.4%, respectively, $P=.01$).

DISCUSSION

This study provides evidence that abnormal brain Doppler before the onset of labor induction indentifies small-for-gestational-age fetuses at high risk of emergency cesarean delivery for nonreassuring fetal status and neonatal acidosis. The data suggest that combination of middle cerebral artery Doppler and cerebroplacental ratio may refine prediction and establish subgroups with progressive risk of nonreassuring fetal status. These findings add to the body of evidence suggesting that the diagnostic category of small for gestational age includes a proportion of cases with true growth restriction and mild placental insufficiency, which is not reflected in the umbilical artery Doppler. In this category, in which longitudinal studies have demonstrated that umbilical artery impedance remains normal throughout the fetal monitoring,[31] brain redistribution seems to constitute a surrogate of placental insufficiency and hypoxia as suggested by its association with abnormal neonatal

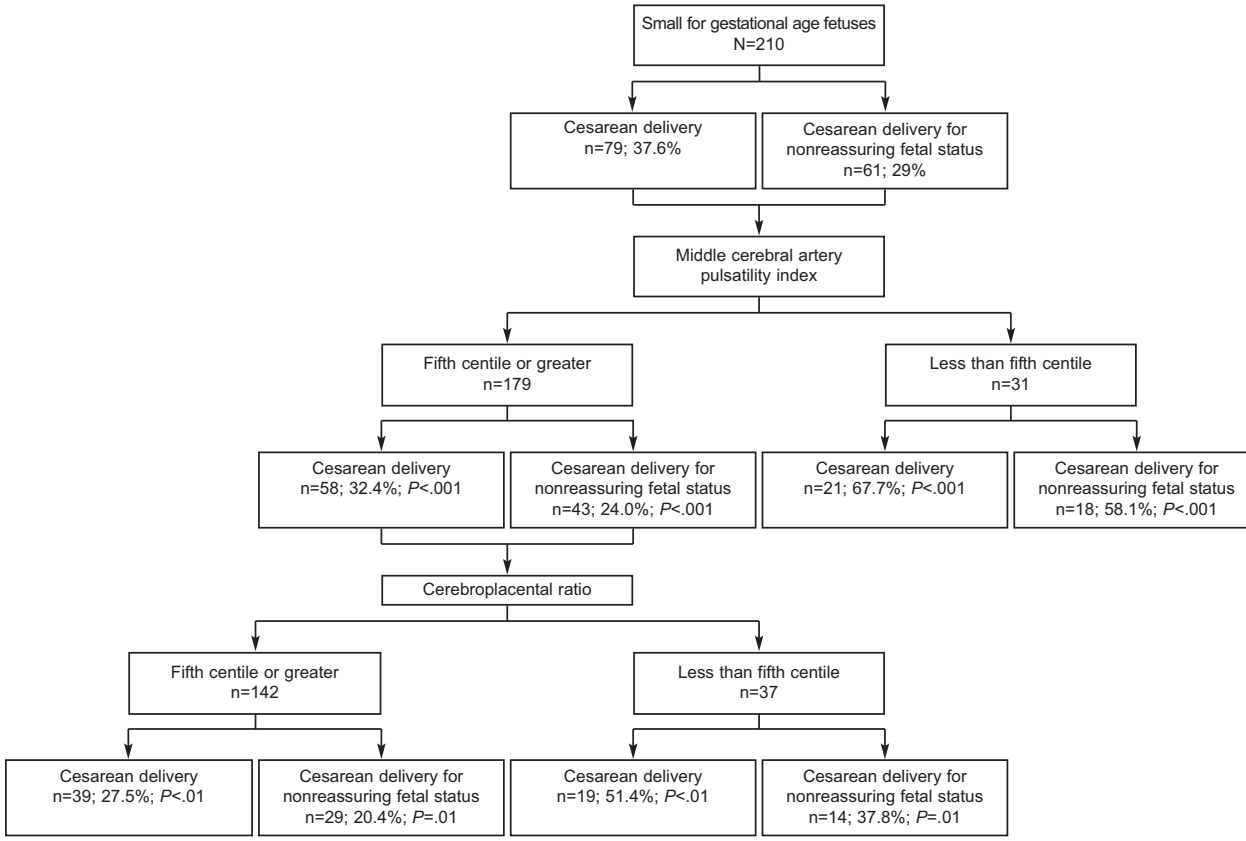

Fig. 4. Clinical algorithm for prediction of intrapartum cesarean delivery ($P<.001$) and cesarean delivery because of nonreassuring fetal status ($P<.001$). Small-for-gestational age fetuses with middle cerebral artery vasodilation had an overall cesarean rate of 67.7% compared with 51.4% in fetuses with normal middle cerebral artery but an abnormal cerebroplacental ratio and compared with 27.5% in fetuses with both normal parameters. The difference was explained by a significant increase in the rate of cesarean delivery because of nonreassuring fetal status (58.1%, 37.8%, and 20.4%, respectively).

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neurobehavior[10,17] The present study suggests a new clinical application for fetal brain Doppler in the selection of small-for-gestational-age fetuses at risk of nonreassuring fetal status during labor induction.

This study found that middle cerebral artery Doppler had the highest value to predict the individual risk of emergency cesarean delivery for nonreassuring fetal status. The data are in line with Severi et al[9] who reported that the risk of cesarean delivery was increased in small-for-gestational-age fetuses with middle cerebral artery vasodilation at the time of diagnosis. Concerning the cerebroplacental ratio, our clinical algorithm shows that decreased cerebroplacental ratio values had a higher sensitivity than middle cerebral artery vasodilation for emergency cesarean delivery for nonreassuring fetal status (45.9% compared with 29.5%) but lower specificity (78.5% compared with 91.3%). These findings are in agreement with previous studies in preterm fetuses with growth restriction showing that cerebroplacental ratio becomes abnormal earlier[32–34] and, thus, it has a greater sensitivity for adverse outcome than middle cerebral artery,[12–15] but it is less specific.[35] As the decision tree algorithm illustrates, combining both middle cerebral artery and cerebroplacental ratio allows an overall detection rate for nonreassuring fetal status of 50% while maintaining a specificity of 76%. Concerning brain tissue perfusion as measured by fractional moving blood volume, this study showed no association with the risk of nonreassuring fetal status or neonatal acidosis. Brain tissue perfusion becomes abnormal earlier than spectral Doppler parameters such as middle cerebral artery and cerebroplacental ratio[16] and has shown the greatest sensitivity to detect poor neonatal neurobehavior among term small-for-gestational-age fetuses.[17] It can be hypothesized that increased brain perfusion by fractional moving blood volume identifies early stages of fetal

hypoxia, when a majority of small-for-gestational-age fetuses are still capable of tolerating uterine contractions. On the contrary, abnormal middle cerebral artery Doppler, which appears only in advanced stages,[16,31] would indicate a lower fetal reserve in the presence of uterine contractions. In agreement with this contention, middle cerebral artery was the only brain Doppler parameter associated with neonatal acidosis, which is a major contributor to neonatal neurological morbidity.[36]

The effect of the identification of small-for-gestational-age fetuses at risk of emergency cesarean delivery after labor induction should not be underestimated. Small for gestational age affects up to 10% of the deliveries in developed countries and represents approximately 400,000 cases per year in the United States.[37] Although there are recommendations that term IUGR fetuses should be monitored during delivery as high-risk pregnancies,[38] there is no consensus about the best strategy for delivery. A recent multicenter clinical trial failed to demonstrate differences in perinatal outcome between expectant management compared with induction of labor.[39] However, this study defined small-for-gestational-age fetuses only by estimated fetal weight percentiles and therefore it remains unclear whether the results might differ in the subgroup of small-for-gestational-age fetuses with signs of late-onset IUGR. The lack of consensus is reflected in a substantial proportion of small-for-gestational-age pregnancies managed by induction of labor.[18–20] These numbers may increase as evidence supporting an increased risk of adverse perinatal and neurodevelopmental outcome in term small-for-gestational-age fetuses accumulates.[2–7] However, labor induction in small for gestational age carries a higher risk of nonreassuring fetal status and emergency cesarean delivery,[9] which in turn are associated with increased maternal and perinatal risks and high resource consumption.[40–42] The results of this study may be of help in decision-making at the time of induction of labor. Brain Doppler may allow identifying patients with high risk of emergency cesarean delivery and overall low chances of successful vaginal delivery. Prediction of this risk before labor induction might allow a better patient-individualized counseling and a more efficient provision of resources in cases of suspected small for gestational age. However, it must be stressed that this study does not intend to suggest a single best management strategy for delivering small-for-gestational-age pregnancies presenting with abnormal brain Doppler. For instance, it cannot be ruled out that poor outcome is strongly influenced by intrauterine environmental factors associated with growth restriction, and thus cesarean delivery would not result in any improvement on long-term outcome. In addition, the answer to this question may be strongly influenced by other factors including cervical conditions, parity, and availability of resources. In any event, the data suggest that brain Doppler may help establishing overall risks that could be combined with other clinical information in decision-making processes and opens opportunities for clinical trials addressing these questions. Multicenter clinical studies including evaluation of the mentioned factors might help refining the appropriate application of fetal brain Doppler evaluation in the selection of cases for trial of labor compared with elective cesarean delivery.

Strengths of this study are the prospective design, the inclusion of a well-defined cohort of term small-for-gestational-age fetuses with normal umbilical artery Doppler exposed to labor induction, and that obstetricians in charge of labor monitoring were blinded to the brain Doppler parameters evaluated in this study. Among the limitations of the study, it must be acknowledged that because all brain Doppler measurements were performed by a single expert, this may limit the external validity and therefore the generalizability of the results, although it increases the internal validity of the study. In addition, the sample size of the study did not allow evaluating the contribution of known factors affecting the risk of cesarean delivery such as Bishop score and parity into the clinical algorithm. The fact that most instances of cesarean delivery for nonreassuring fetal status occurred early in the induction process reduces the potential influence of these factors, but larger studies are needed to address this issue. Finally, we acknowledge that the clinical applicability of these findings may be limited because brain Doppler evaluation in advanced gestational ages requires expertise and this may not be readily available in all settings. In addition, like with other Doppler indices, middle cerebral artery vasodilation must be confirmed over 24 hours to avoid false-positive results.[43]

In conclusion, evaluation of spectral brain Doppler indices allows identification of small-for-gestational-age fetuses with late-onset IUGR and normal umbilical artery Doppler at risk of emergency cesarean delivery for nonreassuring fetal status and metabolic acidosis at birth. These findings support the assessment of brain Doppler in the monitoring of small-for-gestational-age fetuses to improve timely delivery and decision-making regarding induction of labor at term.

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STUDY 6

Cerebral blood perfusion and neurobehavioral performance in full term small for gestational age fetuses

Cruz-Martinez R, Figueras F, Oros D, Meler E, Padilla N, Hernández-Andrade E, Gratacos E.

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OBSTETRICS

Cerebral blood perfusion and neurobehavioral performance in full-term small-for-gestational-age fetuses

Rogelio Cruz-Martinez, MD; Francesc Figueras, PhD; Daniel Oros, MD; Nelly Padilla, MD; Eva Meler, MD; Edgar Hernandez-Andrade, PhD; Eduard Gratacos, PhD

OBJECTIVE: The purpose of this study was to evaluate changes in cerebral blood perfusion and middle cerebral artery (MCA) Doppler in full-term small-for-gestational-age fetuses (SGA) and to explore their association with neonatal neurobehavioral performance.

STUDY DESIGN: Frontal brain perfusion that was measured by fractional moving blood volume (FMBV) and MCA Doppler pulsatility index were assessed in 60 SGA fetuses with normal umbilical artery Doppler results that were matched with adequate-for-gestational-age fetuses. Neonates were evaluated with the Neonatal-Behavioral-Assessment-Scale (NBAS).

RESULTS: The proportion of SGA fetuses with increased FMBV (35% vs 5%; $P < .001$) and decreased MCA Doppler pulsatility index (15% vs 1.7%; $P < .01$) was significantly higher. SGA fetuses showed poorer NBAS scores in all areas. Increased FMBV identified SGA fetuses with the highest risks of abnormal NBAS in social-interactive (odds ratio, 7.8), attention (odds ratio, 22.8), and state-organization (odds ratio, 25.0). Abnormal MCA Doppler identified SGA with abnormal scores in motor area (odds ratio, 10.7).

CONCLUSION: Increased brain blood perfusion discriminates SGA fetuses that are at risk for abnormal neurobehavior.

Key words: cerebral blood perfusion, fractional moving blood volume, middle cerebral artery, Neonatal Behavioral Assessment Scale, small-for-gestational-age

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Intrauterine growth restriction (IUGR) has well-recognized perinatal and long-term consequences. Because not all fetuses that are found to be small in utero have true growth restriction, the distinction of placental insufficiency from constitutional smallness has been 1 of the goals of fetal medicine over the last 20 years. The most widely used sign to identify placental insufficiency and consequently to diagnose IUGR is an elevated pulsatility index (PI) in the umbilical artery (UA).[1,2] Small fetuses with normal UA Doppler findings are defined normally as small-for-gestational-age (SGA), and earlier reports suggested that they essentially might represent constitutionally small fetuses.[3] However, recent evidence suggests that this diagnostic category contains a proportion of cases with true forms of fetal growth restriction, where the degree of placental insufficiency is not reflected in the UA Doppler findings. Thus, studies over the last decade have provided evidence that, on average, SGA fetuses have significantly poorer perinatal outcomes.[4-6] In addition, a considerable proportion of these fetuses show abnormal neurobehavior neonatally[7-9] and abnormal neurodevelopmental tests in childhood,[10] with features similar to those described for children who have IUGR.[11,12] Because the identification of SGA fetuses with true growth restriction cannot be based on UA Doppler findings, assessment of fetal signs such as brain circulation changes could be used for these purposes.[4,13,14]

Chronic fetal hypoxia is associated consistently with increased brain perfusion, which is also defined as brain sparing.[15] In clinical practice, brain sparing is identified by a middle cerebral artery (MCA) Doppler PI below the 5th percentile.[16] Recent studies have demonstrated that a proportion of SGA fetuses with MCA vasodilation have poorer perinatal outcome[4,14] and a higher risk of abnormal neurobehavior neonatally[17] at 2 years of age.[18] These studies support the use of brain Doppler evaluation to distinguish SGA with growth restriction from constitutional smallness. However, vasodilation of the MCA might have a poor sensitivity to detect fetuses in the initial stages of increased brain perfusion. Longitudinal studies on Doppler evaluation of different brain arteries in growth restriction suggest that MCA PI

From the Department of Maternal-Fetal Medicine, Institut Clínic de Ginecologia, Obstetrícia i Neonatologia (ICGON); the Fetal and Perinatal Medicine Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Hospital Clinic–University of Barcelona, Barcelona, Spain.

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Reprints: Eduard Gratacos, PhD, Maternal-Fetal Medicine Department, Hospital Clinic, University of Barcelona, Sabino de Arana 1, 08028 Barcelona, Spain. gratacos@clinic.ub.es.

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is reduced in a later stage than other brain vessels, such as the anterior cerebral artery.[16,19]

Brain tissue perfusion can be estimated reproducibly and reliably with fractional moving blood volume (FMBV), a power Doppler method that has been validated in experimental models and human fetuses.[20,21] Using FMBV, our group has recently demonstrated that frontal brain perfusion increases weeks before the MCA PI is significantly reduced in early-onset IUGR.[22] In this study, we evaluated MCA Doppler evaluation and frontal brain perfusion by FMBV in a cohort of SGA and normally grown fetuses and compared the association of these 2 brain hemodynamic parameters with neonatal neurobehavior.

Materials and Methods

Subjects

A cohort was created of consecutive cases of suspected SGA singleton fetuses that were born at >37 weeks of gestation between December 2007 and November 2008, with confirmed birthweight below the 10th percentile according to local standards.[23] Exclusion criteria were (1) congenital malformations and chromosomopathies and (2) UA PI of >95th percentile.[24] *Adequate-for-gestational-age* (AGA) *control fetuses* were defined as singleton fetuses with a birthweight between the 10th and 90th percentile according to local standards.[23] Control fetuses were selected from our general population, individually matched with cases by gestational age at inclusion (±1 weeks), corrected by first-trimester ultrasound.[25] The protocol was approved by the hospital ethics committee, and written consent was obtained for the study from all the women.

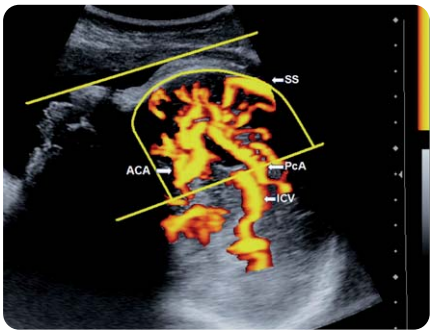
Ultrasound and Doppler measurements

Prenatal Doppler ultrasound examinations were performed weekly with an ultrasound machine (Siemens Sonoline Antares; Siemens Medical Systems, Malvern, PA) that was equipped with a 6-2 MHz linear curved-array transducer. With color directional Doppler scans, the study included (1) UA PI that had been obtained from a free-floating portion of the umbilical cord and (2) MCA PI that had been obtained in a transversal view of the fetal head, at the level of its origin from the circle of Willis. Normal UA was considered to be a PI <95th percentile, and MCA vasodilation was considered to be an MCA PI <5th percentile.[24] Doppler recordings were performed in the absence of fetal movements and voluntary maternal suspended breathing. Pulsed Doppler parameters were performed automatically from ≥3 consecutive waveforms, with the angle of insonation as close to 0 as possible. A high-pass wall filter of 70 Hz was used to record low flow velocities and to avoid artifacts. Only the last examination within 1 week of delivery was included in the analysis. Labor induction was performed at term for the cases with an estimated fetal weight <3rd percentile by cervical ripening. Delivery was attended by a staff obstetrician.

Cerebral blood perfusion

With power Doppler ultrasound, frontal brain perfusion was evaluated weekly in a sagittal view of the fetal head. Only the last examination within 1 week of delivery was included in the analysis. Control fetuses were evaluated at the same gestational age as cases, according to our matched design. In a midsagittal view of the fetal brain, the power Doppler color box was placed to include all the frontal part of the brain. Five consecutive high-quality images with no artifacts were recorded with the use of the following fixed ultrasound setting: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1, and pulsed repetition frequency of 610 Hz. All images were examined offline, and FMBV was estimated with the statistical software (MATLAB version 7.5; The MathWorks, Natick, MA), as previously described.[26] The mean FMBV from all 5 images was considered to be representative for that specific case and was expressed as percentage. The region of interest was delineated as described elsewhere[20]; anteriorly by the internal wall of the skull, inferiorly by the base of the skull, and posteriorly by an imaginary line drawn at 90 degrees at the level of the origin of the anterior cerebral artery and parallel to an imaginary line in the front of the face (Figure 1). Frontal FMBV was converted into percentiles according to normal reference ranges that were obtained previously from 92 AGA fetuses. Increased frontal perfusion was considered to be an FMBV of >95th percentile.

FIGURE 1



Frontal perfusion's power Doppler image.

ACA, anterior cerebral artery; *ICV*, internal cerebral vein; *PcA*, pericallosal artery; *SS*, sagittal sinus.

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Neurobehavioral performance

The Neonatal Behavioral Assessment Scale (NBAS) was performed prospectively in all cases and control fetuses at 40 ± 1-week corrected age by 1 of 3 observers who were accredited by The Brazelton Institute (Harvard Medical School, Boston, MA). The observers were blinded to the study group and to the Doppler status. The examination consisted of 6 behavioral areas rated on a 1-9 scale, where 9 is the best performance for some areas and for others this is represented by the central score of 5.[27]

With the newborn infant between 2 feedings in a small and semidark quiet room with a temperature between 22-27°C and in the presence of at least 1 parent, the following areas were analyzed: social-interactive (which includes response to visual and acoustic stimuli), organization of state (which includes peak of excitement, rapidity of build-up, irritability, and lability of states), and motor (which includes general tone, motor maturity, pull-to-sit, defensive movements, and level of activity). After a recent report by the original authors of the NBAS, individual items were clustered to assess the attention capacity

TABLE 1
Clinical characteristics of the study groups

Variable	Adequate-for-gestational-age (n = 60)	Small-for-gestational-age (n = 60)	*P* value[a]
Gestational age at ultrasound, wk[b]	37.8 ± 1.0	38.0 ± 1.3	.42
Maternal age, y[b]	31.6 ± 4.8	31.5 ± 5.0	.78
Low socioeconomic class, %[c]	38.3	58.3	.03
Primiparity, %	63.3	68.3	.44
Nonwhite ethnicity, %	26.7	13.3	.07
Smoking, %	18.3	23.3	.50
1-10 cigarettes/d	15	18.3	.62
10-19 cigarettes/d	1.7	3.3	.56
≥20 cigarettes/d	1.7	1.7	1.00
Labor induction, %	40	65	.006
Cesarean section delivery, %	20	28.3	.29
Gestational age at delivery, wk[b]	38.8 ± 1.0	38.5 ± 1.3	.13
Birthweight, g[b]	3170 ± 407	2418 ± 245	< .001
Birthweight percentile, %[b]	41.9 ± 24.9	5.0 ± 3.6	< .001
Male/female ratio, n_0/n_1	31/29	32/28	.86
5-minute Apgar score <7, n	0	0	—
Admission in the neonatal unit, d	0	0.75 ± 2.2	.01
Postnatal days at test performance, d[b]	11.59 ± 12.2	13.91 ± 11.7	.33

[a] Student *t* test for independent samples or Pearson-χ^2 test; [b] data are expressed as mean ± SD; [c] routine occupations, long-term unemployment, or never worked (UK National Statistics Socio-Economic Classification).

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(which includes alertness, quality of alert responsiveness, and cost of attention).[28] The behavioral items were converted into percentiles according to normal curve references for our population,[29] and each area was considered abnormal at a score <5th percentile.

Statistical analysis

The Student *t* test or 1-way analysis of variance and Pearson χ^2 test were used to compare quantitative and qualitative data, respectively. With the use of standard methods, neurobehavioral outcome was adjusted for smoking during pregnancy (no smoking; 1-9 cigarettes/d; ≥10 cigarettes/d), ethnicity (white vs nonwhite), low socioeconomic status, labor induction, mode of delivery (cesarean section vs vaginal delivery), gestational age at birth, gender, postnatal days at evaluation, and days of admission in the neonatal unit[27,30,31] by multiple linear or logistic regression. Statistical analysis was performed with statistical software (SPSS version 15.0; SPSS Inc, Chicago, IL).

RESULTS

A total of 66 consecutive cases who fulfilled the inclusion and exclusion criteria were studied. In 6 cases, frontal brain perfusion could not be evaluated because of the degree of engagement of the fetal head into the pelvis, which left 60 cases for the analysis that were matched with 60 control fetuses, which resulted in a final population of 120 fetuses.

Table 1 shows the maternal and neonatal clinical characteristics of the population. According to our matched design, gestational age at inclusion was similar between cases and control fetuses. No differences were observed between maternal smoking, mode of delivery, gender, and postnatal days at NBAS evaluation. Mothers in the SGA group were more frequently from a low socioeconomic level (58.3% vs 38.3%). Labor induction was more frequent in the SGA group (65% vs 40%).

SGA fetuses showed significantly higher mean frontal FMBV values than AGA fetuses (17.72% ± 6.8% vs 12.97% ± 4.3%; $P < .001$). The proportion of fetuses with an increase in FMBV values of >95th percentile was 35% in the SGA group, compared with 5% in the control group ($\chi^2 = 16.9$; $P < .001$). The proportion of fetuses with MCA PI <5th percentile was 15% in SGA fetuses and 1.7% in AGA fetuses ($\chi^2 = 6.9$; $P < .01$).

Table 2 shows the NBAS score by areas in the study groups. All neurobehavioral areas that were studied had significantly lower scores in the SGA group. The differences remained statistically significant after adjustment for potential confounders (maternal smoking, ethnicity, socioeconomic status, labor induction, mode of delivery, gestational age at delivery, gender, postnatal days at test performance, and days of admission in the neonatal unit).

TABLE 2
Neurobehavioral performance by study group

Variable	Adequate-for-gestational-age (n = 60)	Small-for-gestational-age (n = 60)	*P* value[a]	*P* value[b]
Social-interactive	6.53 ± 1.3	5.92 ± 1.7	.039	.033
Attention capacity	6.83 ± 1.1	6.10 ± 1.5	.006	.028
Organization of state	4.67 ± 0.9	4.07 ± 1.3	.010	.048
Motor	5.77 ± 0.6	5.46 ± 0.9	.047	.020

Results are expressed as mean ± SD.

[a] Student *t* test; [b] adjusted for maternal smoking, ethnicity, socioeconomic status, labor induction, mode of delivery, gestational age at delivery, gender, postnatal days at test performance, and days of admission in the neonatal unit by multiple linear regression.

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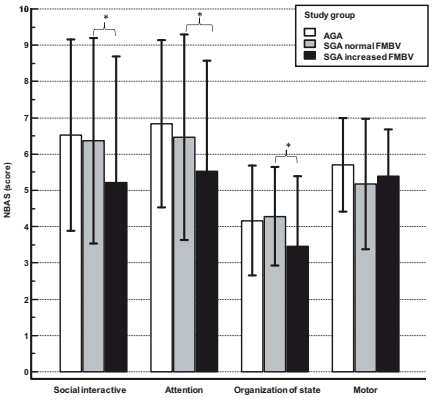
The association of increased frontal FMBV or reduced MCA PI with the NBAS scores was explored. Figure 2 summarizes the mean NBAS score for AGA fetuses and for SGA fetuses that were divided into 2 groups, with and without increased frontal brain perfusion. Among SGA fetuses, cases with increased FMBV showed significantly lower NBAS in social-interactive, attention, and organization of state areas than the control group. In contrast, SGA fetuses with normal FMBV had NBAS values similar to control fetuses. Likewise, the frequency of fetuses with abnormal NBAS increased linearly and significantly when SGA fetuses were classified according to the presence of absence of increased frontal brain perfusion (Figure 3). Odds ratios for abnormal NBAS in SGA fetuses with and without increased perfusion are displayed in Table 3. When the association of MCA PI with NBAS was explored, SGA cases with abnormal MCA PI showed significantly lower NBAS in the motor area with an adjusted odds ratio of 10.72 (95% confidence interval, 1.57–73.32; $P = .016$; Figure 4).

FIGURE 2



NBAS by study group and FMBV.

AGA, appropriate-for-gestational-age; *FMBV*, fractional moving blood volume; *NBAS*, Neonatal Behavioral Assessment Scale; *SGA*, small-for-gestational-age.
The *asterisk* denotes a probability value of < .05.

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Comment

We have demonstrated previously that early-onset IUGR fetuses with Doppler signs of placental insufficiency have increased frontal perfusion from earlier stages of fetal deterioration.[22] In this study, we extended this observation to SGA fetuses with normal UA Doppler findings and provided evidence that 35% of these fetuses have increased frontal brain perfusion. These findings are consistent with the notion that a proportion of SGA fetuses experience hypoxia in utero. Furthermore, the results of this study suggest that evaluation of increased brain tissue perfusion discriminates fetuses that are at risk for abnormal neurobehavioral performance with a much higher sensitivity than MCA Doppler evaluation.

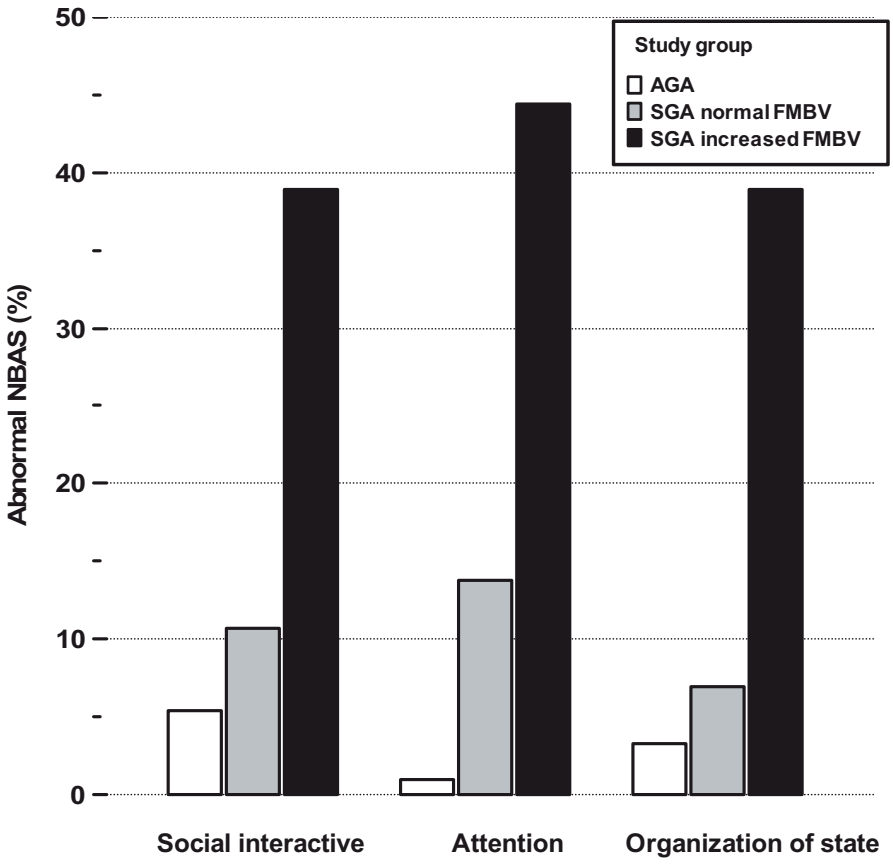
Our findings confirm previous studies on the existence of a significantly increased risk of abnormal neurobehavior in SGA infants.[7-9] Previous neonatal neurobehavioral studies showed that SGA infants scored significantly lower in state organization, orientation to social and nonsocial stimuli, and motor domains, compared with AGA children neonatally.[7,11] These neonatal data are consistent with longer term follow-up studies that have demonstrated neurodevelopmental differences at 2 years of age.[8,11] Concerning brain hemodynamics, there are no previous studies that have assessed the relationship between MCA Doppler and tissue perfusion with neonatal neurobehavior. In any event, our results are in line with long-term follow-up studies that show an association between MCA vasodilatation and suboptimal neurodevelopment in preterm[32,33] and term SGA fetuses.[18]

The performance of MCA Doppler evaluation was considerably worse than that of FMBV to predict abnormal neurobehavior. MCA vasodilation was associated only with abnormal motor behavior, although there were nonsignificant trends for most of the associations that were studied. It therefore cannot be excluded that our study was underpowered to detect such associations. Our findings support that frontal FMBV is a more sensitive parameter than MCA PI to identify increased brain perfusion and subtle degrees of neurologic injury. These findings are consistent with previous studies about regional brain perfusion in human fetuses with growth restriction, in which the onset of increased brain perfusion occurred long before a reduction in MCA PI <5th percentile was reached. Actually, established vasodilation of the MCA seemed to coincide with a decline in the relative perfusion to the frontal lobe in relation with other regions, such as the basal ganglia.[22] Thus, a reduction in MCA PI indicates a relatively ad-

vanced stage in the establishment of increased brain blood flow, which may explain the reduced sensitivity of this vessel in comparison with direct measurements of fetal cerebral blood perfusion.

The data that have been provided by this study add to the body of evidence that suggests that increased brain perfusion is not an entirely protective mechanism. During the second half of gestation, profound changes in brain organization take place that involve critical neural connections and myelination of important neural tracts.[34] It is not known how the susceptibility of the brain changes as such maturation progresses, but it is plausible that even mild degrees of hypoxia can induce permanent epigenetic changes that are the result of the adaptation of the developing brain to a hypoxic and undernourished environment. The frontal brain seems to be a particularly susceptible structure in growth restriction. Recent studies that have used magnetic resonance imaging have demonstrated significant differences in the gray matter volume of several brain areas in children with early-onset IUGR, compared with normally grown very preterm children.[12] The existence of differences in the frontal lobe and the thalami has also been demonstrated in fetuses by 3-dimensional ultrasound in utero.[35] These structural differences are in line with long-term follow-up studies that have suggested that children with mild growth restriction have significant differences in several cognitive competencies.[36] One potential explanation is that the frontal areas are phylogenetically recently acquired; therefore, maturation and myelinization processes of these areas occur late in fetal development, making these structures vulnerable during a long period.[37] In this study, the motor function was associated only with MCA Doppler evaluation and not with frontal tissue perfusion. One could speculate, as a possible explanation, that motor capabilities are highly related with basal ganglia areas, which are supplied directly by the MCA. In contrast, the role of the frontal area is related mainly with instinctual behavior, attention, irritability, impulsiveness, and hyperreactivity.[38]

FIGURE 3



Frequency of abnormal neurobehavioral performance.

AGA, appropriate-for-gestational-age; *FMBV*, fractional moving blood volume; *NBAS*, Neonatal Behavioral Assessment Scale; *SGA*, small-for-gestational-age.

Cruz-Martinez. Cerebral blood perfusion and neurobehavioral performance. Am J Obstet Gynecol 2009.

From a clinical perspective, the results of this study support the notion that brain perfusion could be used as a means to distinguish SGA fetuses with true hypoxia from constitutional smallness. We acknowledge that the clinical application of our findings is limited because there are currently no clinical methods available to measure tissue brain perfusion accurately. Some tools that are now incorporated into commercial devices have substantial limitations in the estimation of perfusion because of a lack of correction for attenuation and depth.[39] However, it is expected that future commercial software tools will incorporate algorithms, such as those used in FMBV estimates. The impact of the identification of SGA fetuses that are at risk for abnormal neurodevelopment cannot be underestimated, considering that the proportion of fetuses that are affected with SGA ranges from 5-8% in developed countries. In preterm infants, individualized developmental interventions have been demonstrated to improve short-term neurobehavioral dysfunction.[40] Whether interventions could be effective in term infants and whether they would influence long-term outcome are unknown. Nevertheless, identifying those at-risk infants is essential to understand the association between fetal well-being and later neurodevelopmental problems and lays the basis for possible preventive interventions. The study has several limitations. First, as any imaging method, FMBV is an indirect estimate of blood perfusion. However, the technique has shown an excellent correlation with gold standards in the estimation of true tissue perfusion in animal experiments.[21] The method has

TABLE 3
Risk of abnormal NBAS by FMBV

	Normal fractional moving blood volume			Increased fractional moving blood volume		
Dependent variable	Odds ratio[b]	95% CI	*P* value[a]	Odds ratio	95% CI	*P* value[a]
Social-interactive	1.20	0.11–13.31	.882	7.82	1.32–46.53	.024
Attention capacity	0	0	.999	22.78	3.87–134.1	.001
Organization of state	2.89	0.27–30.6	.377	25.02	2.73–229.7	.002
Motor	4.04	0.27–60.88	.313	0.974	0.07–13.69	.985

CI, confidence interval; *FMBV*, fractional moving blood volume; *NBAS*, Neonatal Behavioral Assessment Scale.

[a] Adjusted for maternal smoking, ethnicity, socioeconomic status, labor induction, mode of delivery, gestational age at delivery, gender, postnatal days at test performance, and days of admission in the neonatal unit by multiple logistic regression; [b] Referenced to the control group.

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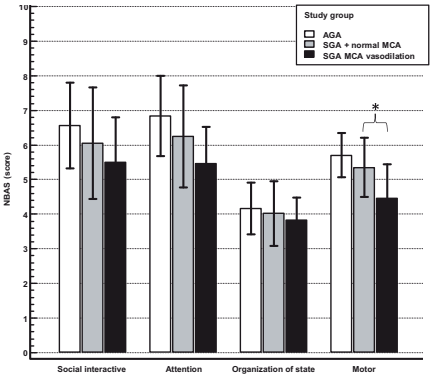
also shown good reproducibility in the assessment of fetal brain perfusion in different regions.[20] Second, although NBAS is a gold standard to evaluate the neonate's capacity to respond to the environment and reflects brain maturation, it only assesses neurobehavior and not cognitive function.[41] However, the early neonatal period offers the unique opportunity to observe neurobehavior and neuromaturation at a time when surrounding influences are still minimal. Several studies have demonstrated the correlation between neonatal neurobehavioral performance and later neurocognitive development. Feldman and Eidelman[11] studied the correlation of neurobehavioral and later cognitive function with the Bayley Scale of Infant Development in SGA premature neonates. They found that neonatal motor maturity correlated with the psychomotor development outcome at 2 years of age. Another interesting study in full-term healthy babies reported that levels of self-regulation were also correlated with the infants' levels of cognitive development (personal-social development, speech development, and eye and hand coordination, which are subvariables in Griffiths' Mental Development Test) and with sleeping disorders at 2 years of age.[42] We acknowledge that the reported results on neonatal neurobehavior must be confirmed with long-term follow-up studies, which are currently underway.

In conclusion, a proportion of SGA fetuses with normal UA Doppler results have higher frontal perfusion than AGA fetuses. Increased perfusion in the frontal lobe discriminates SGA fetuses that are at high risk of abnormal neurobehavioral performance with a much higher accuracy than Doppler evaluation of the MCA. If these findings are confirmed by further studies, the assessment of tissue brain perfusion could be a useful clinical tool for the distinction between true growth restriction and constitutional smallness in fetuses that are now diagnosed as SGA. ■

FIGURE 4



NBAS by study group and MCA vasodilation.

AGA, appropriate-for-gestational-age; *FMBV*, Fractional moving blood volume; *MCA*, middle cerebral artery; *NBAS*, Neonatal Behavioral Assessment Scale; *SGA*, small-for-gestational-age. The *asterisk* denotes a probability value of $< .05$.

Cruz-Martinez. Cerebral blood perfusion and neurobehavioral performance. Am J Obstet Gynecol 2009.

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6. RESULTS

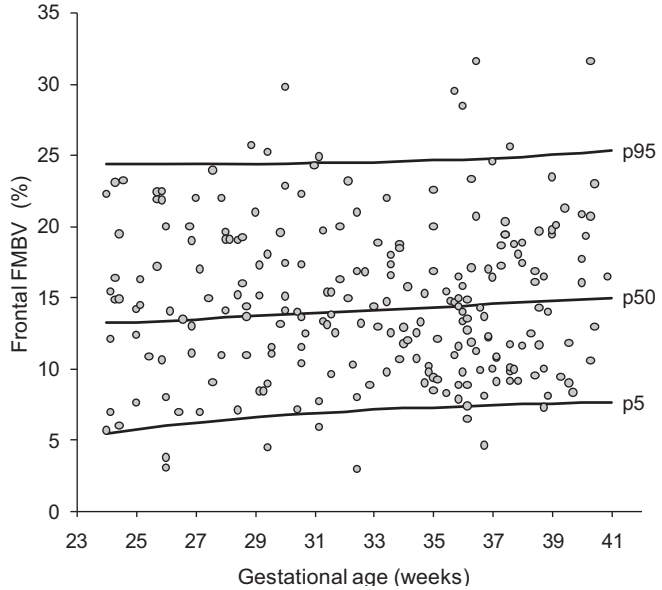
6.1 Study 1: Normal ranges of fetal cerebral blood perfusion

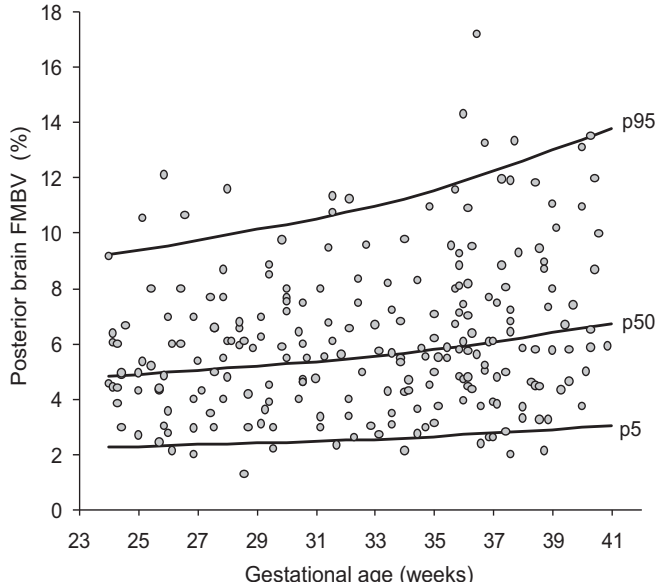
The results of this project have been published in an international journal.
A prospective cohort was created with consecutive singleton fetuses including 12 cases for each week of gestation, between 24 to 41 weeks, corrected by first trimester ultrasound (Robinson and Fleming, 1975), with estimated fetal weight between the 10^{th} and 90^{th} percentile according to local standards (Figueras et al., 2008b).

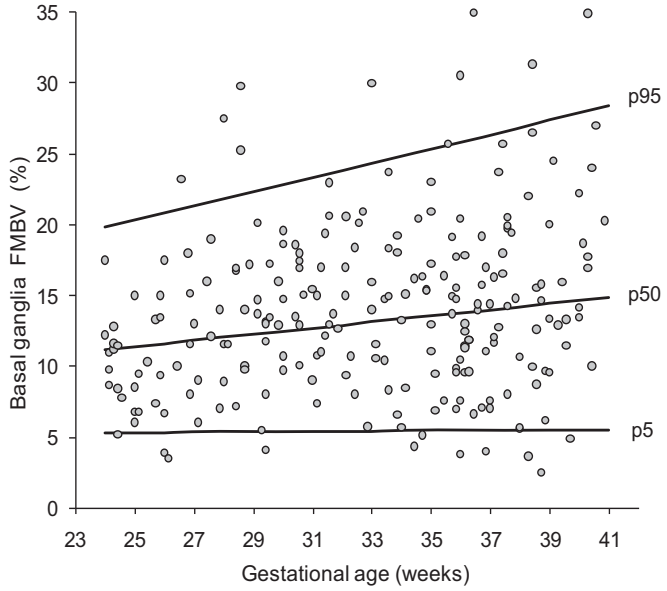
A total of 238 fetuses were included. Cerebral blood perfusion in the basal ganglia and posterior brain were successfully obtained in all examinations, while frontal tissue perfusion could not be obtained in eight cases above 38 weeks of gestation. Thus, a final population of 230 fetuses was analyzed, in whom the median gestational age at inclusion and at delivery was 33.1 (range, 24.0-41.4) and 39.7 (range, 34.9-42.3) weeks, respectively.

For the frontal area, the degrees of freedom used in fitting the cubic splints were 5, 12 and 6 for the L, M and S curves, respectively. The values were 5, 10 and 7; and, 4, 10 and 8, for the basal ganglia and posterior brain regions, respectively.

The next figure depicts the estimated mean and percentile curves for each area studied across gestational age. With advancing gestation, brain tissue perfusion slightly increased in the basal ganglia and posterior brain, whereas frontal tissue perfusion remained stable during pregnancy.


Frontal FMBV (%)
Gestational age (weeks)
p95
p50
p5


Posterior brain FMBV (%)
Gestational age (weeks)
p95
p50
p5


Basal ganglia FMBV (%)
Gestational age (weeks)
p95
p50
p5

The next table shows the gestational-age-related reference ranges and the 5th (p5) and 95th (p95) percentiles for regional cerebral blood perfusion in the three explored areas. The basal ganglia showed the highest FMBV values, followed by the frontal lobe and posterior brain, respectively.

GA (weeks)	Cerebral blood perfusion by FMBV (%)								
	Frontal lobe			Basal ganglia			Posterior brain		
	p5	Mean	p95	p5	Mean	p95	p5	Mean	p95
24	5.39	13.21	24.38	5.32	11.17	19.86	2.24	4.83	9.21
25	5.69	13.23	24.39	5.33	11.39	20.35	2.27	4.90	9.36
26	5.95	13.24	24.39	5.34	11.61	20.83	2.29	4.96	9.53
27	6.18	13.45	24.39	5.36	11.82	21.32	2.32	5.03	9.71
28	6.38	13.56	24.40	5.37	12.04	21.82	2.36	5.11	9.91
29	6.56	13.66	24.41	5.39	12.26	22.31	2.39	5.19	10.11
30	6.72	13.77	24.41	5.39	12.48	22.81	2.42	5.27	10.31
31	6.86	13.88	24.43	5.41	12.69	23.31	2.46	5.36	10.51
32	6.99	13.99	24.46	5.41	12.91	23.81	2.49	5.44	10.73
33	7.10	14.10	24.50	5.43	13.13	24.31	2.53	5.53	10.96
34	7.20	14.21	24.55	5.43	13.34	24.82	2.58	5.64	11.22
35	7.28	14.32	24.62	5.45	13.56	25.32	2.63	5.77	11.53
36	7.36	14.43	24.69	5.45	13.78	25.83	2.70	5.91	11.88
37	7.43	14.54	24.78	5.46	13.99	26.35	2.76	6.06	12.23
38	7.49	14.65	24.88	5.46	14.21	26.86	2.83	6.21	12.60
39	7.54	14.76	25.00	5.46	14.43	27.38	2.89	6.37	12.98
40	7.59	14.86	25.14	5.46	14.64	27.89	2.96	6.53	13.37
41	7.63	14.97	25.30	5.47	14.86	28.41	3.03	6.70	13.77

6.2 Project 2: Normal references ranges of left modified myocardial performance index in near-term fetuses

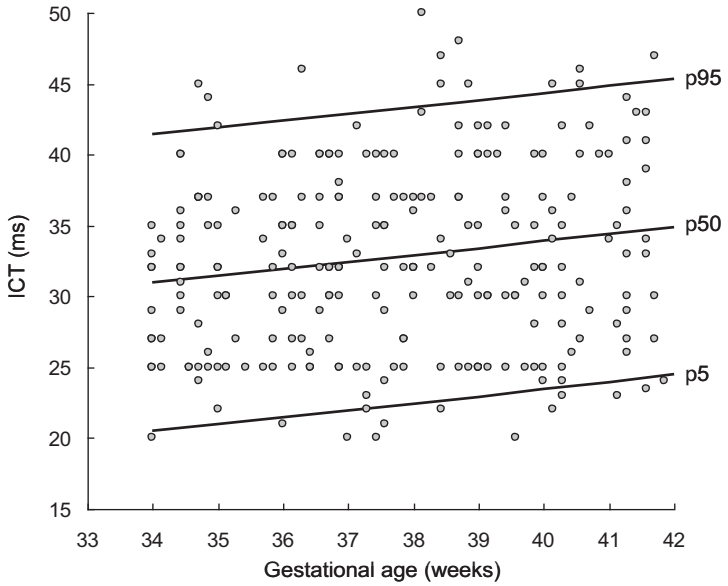
During the study period a total of 245 fetuses were included including 30 cases for each week of gestation, between 34 to 42 weeks, corrected by first trimester ultrasound (Robinson and Fleming, 1975), with estimated fetal weight between the 10th and 90th percentile according to local standards (Figueras et al., 2008b). The MPI was successfully obtained in all examinations regardless of fetal position.

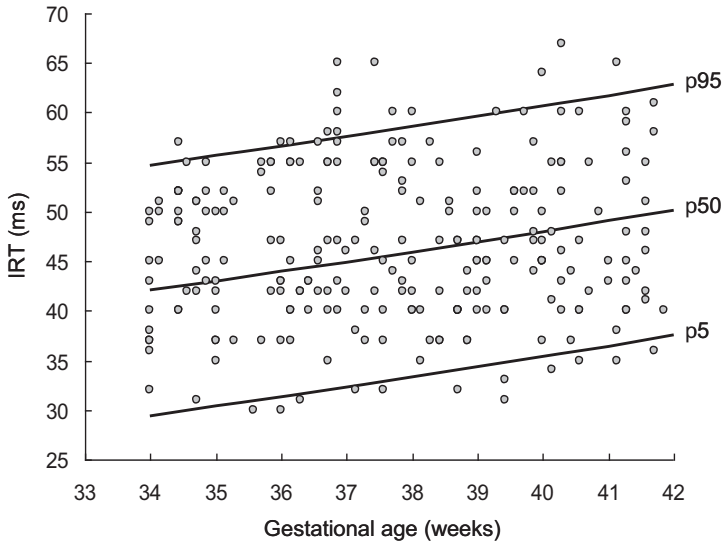
The best parametrical model for all the studied parameters was a first degree lineal polynomial. This table shows the normal reference ranges for the MPI and its individual components including the mean and the 5th and 95th percentile for each gestational age.

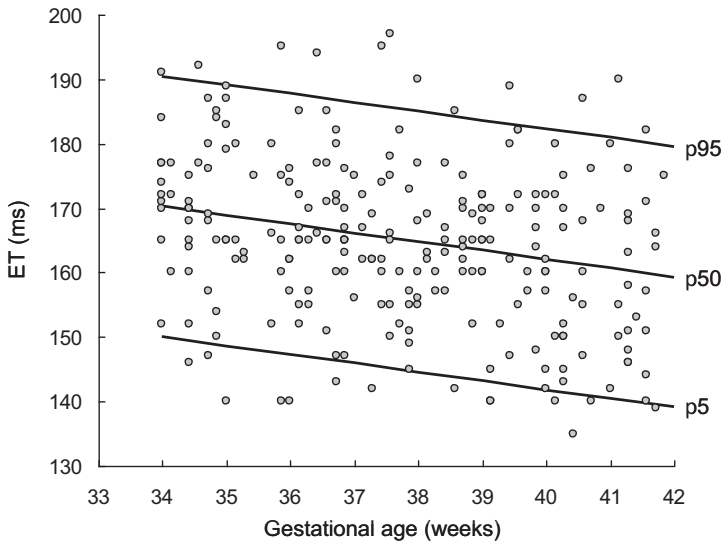
GA	MPI			ICT			IRT			ET		
	p5	p50	p95	p5	p50	p95	p5	p50	p95	p5	p50	p95
34	0,33	0,46	0,58	20,5	31,0	41,4	29,4	42,1	54,7	150	170	190
36	0,34	0,46	0,59	21,0	31,4	41,9	30,3	43,0	55,6	149	169	189
37	0,35	0,47	0,60	21,5	31,9	42,4	31,3	43,9	56,6	147	168	188
38	0,35	0,48	0,61	21,9	32,4	42,8	32,3	44,9	57,6	146	166	186
39	0,36	0,49	0,62	22,4	32,9	43,3	33,3	45,9	58,6	144	165	185
40	0,37	0,50	0,62	22,9	33,4	43,8	34,3	46,9	59,6	143	163	184
41	0,38	0,51	0,63	23,4	33,9	44,3	35,3	48,0	60,6	142	162	182
42	0,39	0,52	0,64	23,9	34,4	44,8	36,4	49,1	61,7	140	161	181

The next figures illustrate a scatter plot with the estimated mean and percentile curves for each studied parameter across gestational age.

All the studied variables showed a progressive change with advancing gestation. From 34 to 42 weeks of gestation, the mean MPI increased from 0.46 to 0.53 (MPI=exp((0.018xGA(weeks))-1.39)) with a constant SD of 0.08. Similarly, the ICT increased from 31 to 35 ms (ICT=exp ((0.015xGA(weeks)-2.92); SD=6.4ms), the IRT increased from 42 to 50ms (IRT=exp ((0.022xGA(weeks)-2.99); SD=7.7 ms) and the ET decreased from 170 to 159ms (ET=216.7- 1.37xGA(weeks); SD=12.3ms).


ICT (ms)
50
45
40
35
30
25
20
15
p95
p50
p5
33
34
35
36
37
38
39
40
41
42
Gestational age (weeks)


IRT (ms)
70
65
60
55
50
45
40
35
30
25
p95
p50
p5
33
34
35
36
37
38
39
40
41
42
Gestational age (weeks)


ET (ms)
200
190
180
170
160
150
140
130
p95
p50
p5
33
34
35
36
37
38
39
40
41
42
Gestational age (weeks)

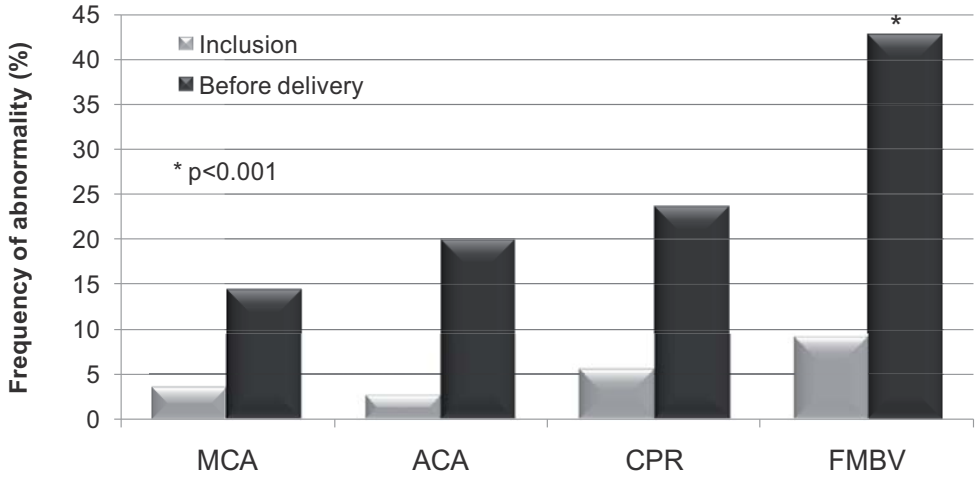
6.3 Project 3: Longitudinal changes of cerebral blood perfusion

The results of this project have been published in an international journal and have been presented at the 8th World Congress in Fetal Medicine, Fetal Medicine Foundation of London, 28 June-2 July 2009 in Portorose, Slovenia; and at the 19th World Congress on Ultrasound in Obstetrics and Gynecology, 13-17 September 2009 in Hamburg, Germany. (oral communication: Cruz-Martinez R*, Figueras F, Meler E, Hernandez-Andrade E, Gratacós E. Longitudinal changes in cerebral blood perfusion in full-term small-for-gestational-age fetuses*).

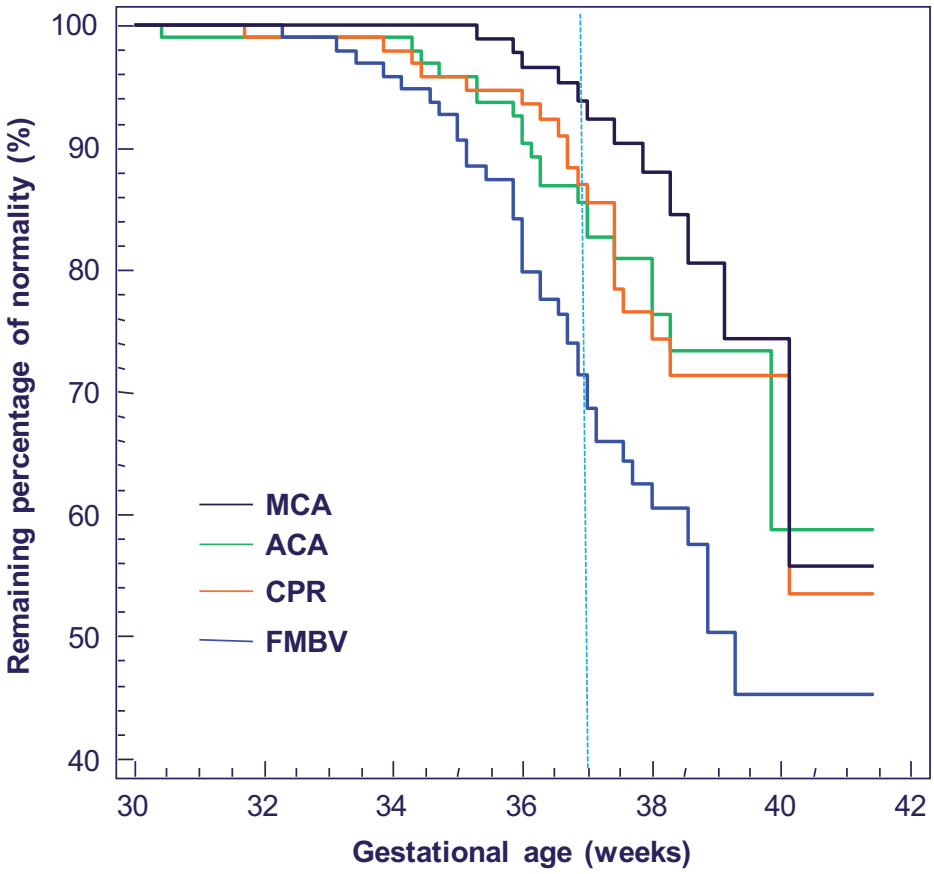
During the study period a total of 307 scans were performed on 110 SGA fetuses. UA, MCA and ACA were successfully obtained in all examinations, while frontal brain perfusion could not be obtained in four examinations due to the degree of engagement of the fetal head into the pelvis.

The median gestational age at inclusion and at delivery was 35.7 (range, 29.4-38.4) and 38.6 (range 37.0-41.9) weeks, respectively. The median interval between the last examination and delivery was 2 (range 0-8) days.

At inclusion, the proportion of cases with abnormal MCA PI, CPR, ACA PI and FMBV was 3.6% (n=4), 5.5% (n=6), 2.7% (n=3) and 9.1% (n=10), respectively. No significant differences were observed between these proportions. At last examination before delivery, the proportion of increased FMBV (42.7%) was significantly higher than the proportion of abnormal MCA PI (16.4%; p <0.01), abnormal CPR (23.6%; p <0.01) and abnormal ACA PI (20.9%; p<0.01).



This figure shows the survival graph of the Doppler parameters throughout the study period, plotted against gestational age, which could be interpreted as the remaining proportion of normal MCA PI, ACA PI, CPR and FMBV at each week of gestational age.



At 37 weeks, the proportion of abnormal values was 10.8% (95% CI 4.1-17.4) for the MCA PI, 16.8% (95% CI 8.7-24.9) for the CPR, 17.2% (95% CI 9.3-25.4) for the ACA PI and 31.3% (95% CI 21.5-41.0) for the FMBV. Similarly, the first quartile survival time (when a quarter of the population had abnormal Doppler) occurred at 39.14 weeks (95% CI 38.1-40.2) for the MCA, at 38.3 weeks (95% CI 37.0-39.5) for the CPR, 38.3 weeks (95% CI 37.0-39.5) for the ACA and 36.7 weeks (95% CI 36.0-37.4) for the FMBV.

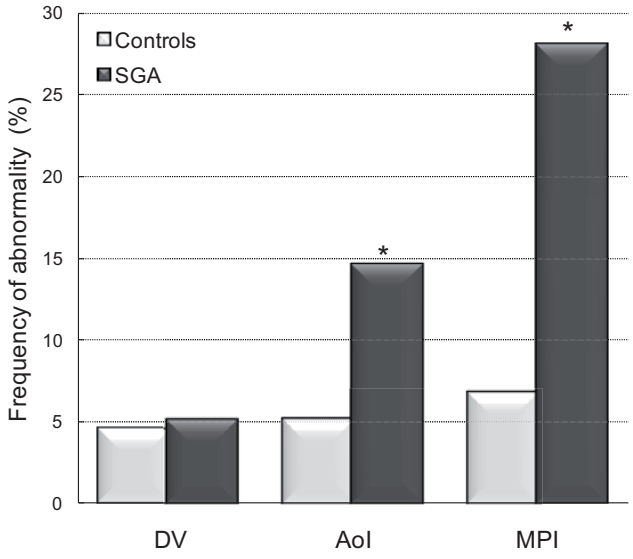
6.4 Project 4: Changes of fetal cardiac Doppler parameters

Study population

Myocardial performance index (MPI), aortic isthmus (AoI) and ductus venosus (DV) pulsatility indices were measured within one week of delivery in a cohort of 178 term singleton consecutive SGA fetuses with normal umbilical artery PI (<95th percentile) and 178 controls.

While no differences were observed in DV PI, SGA fetuses showed significantly higher mean MPI values (0.56 vs. 0.49; t=6.8; p<0.01) and AoI PI (3.84 vs. 2.87; t=3.6; p<0.01) than controls.

This figure shows the proportion of cases with abnormal Doppler parameters (above the 95th percentile) by study groups. The rate of cases with abnormal DV PI was similar between cases and controls. However, SGA fetuses had more frequently abnormal MPI values (28.1% vs. 6.7%; χ^2=28.2, p<0.01). Similarly, the proportion of fetuses with abnormal AoI PI was 14.6% in the SGA group and 5.1% in controls (χ^2=9.1, p<0.01).



AoI retrograde net blood flow was observed in 7.3% of the SGA fetuses and in none of the controls (Fisher's exact test p<0.01). Of note, the proportion of abnormal MPI was significantly higher than the proportion of abnormal AoI PI (28.1% vs. 14.6%; Mc Nemar p<0.01).

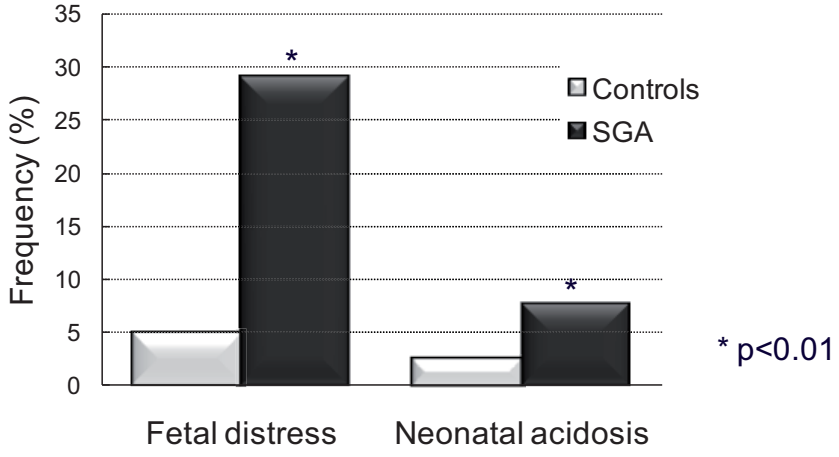
6.5 Project 5: Prediction of fetal distress and neonatal acidosis

The results of this project have been accepted in an international journal and have been presented at the 9th World Congress in Fetal Medicine and the Eurofoetus Meeting of the Fetal Medicine Foundation of London, 20-24 June 2010 in Rhodes, Greece; and in the 20th World Congress on Ultrasound in Obstetrics and Gynecology, 10-14 October 2010 in Prague, (Oral communication: *Cruz-Martinez R, Gratacós E. Prediction of emergency cesarean section for fetal distress in term small-for-gestational-age fetuses with Doppler signs of brain sparing.*).

Study population

During the study period a total of 223 consecutive SGA cases fulfilling the inclusion and exclusion criteria were studied. In 13 cases (5.8%) frontal brain perfusion could not be evaluated due to the degree of engagement of the fetal head into the pelvis, leaving 210 cases for the analysis that were matched with 210 controls, resulting in a final population of 420 fetuses. In all cases, only the last examination within 24 hours before the onset of labor induction was included in the analysis.

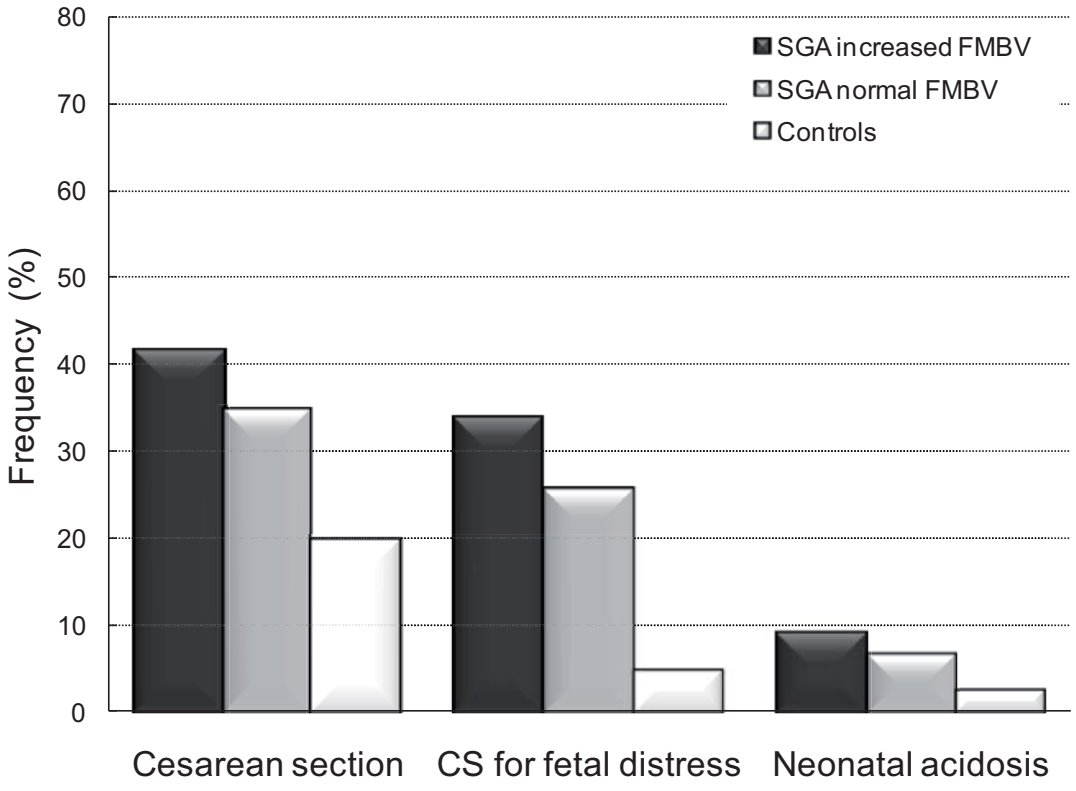
SGA fetuses showed a significantly higher rate of CS, emergency CS due to FD and neonatal acidosis than controls.



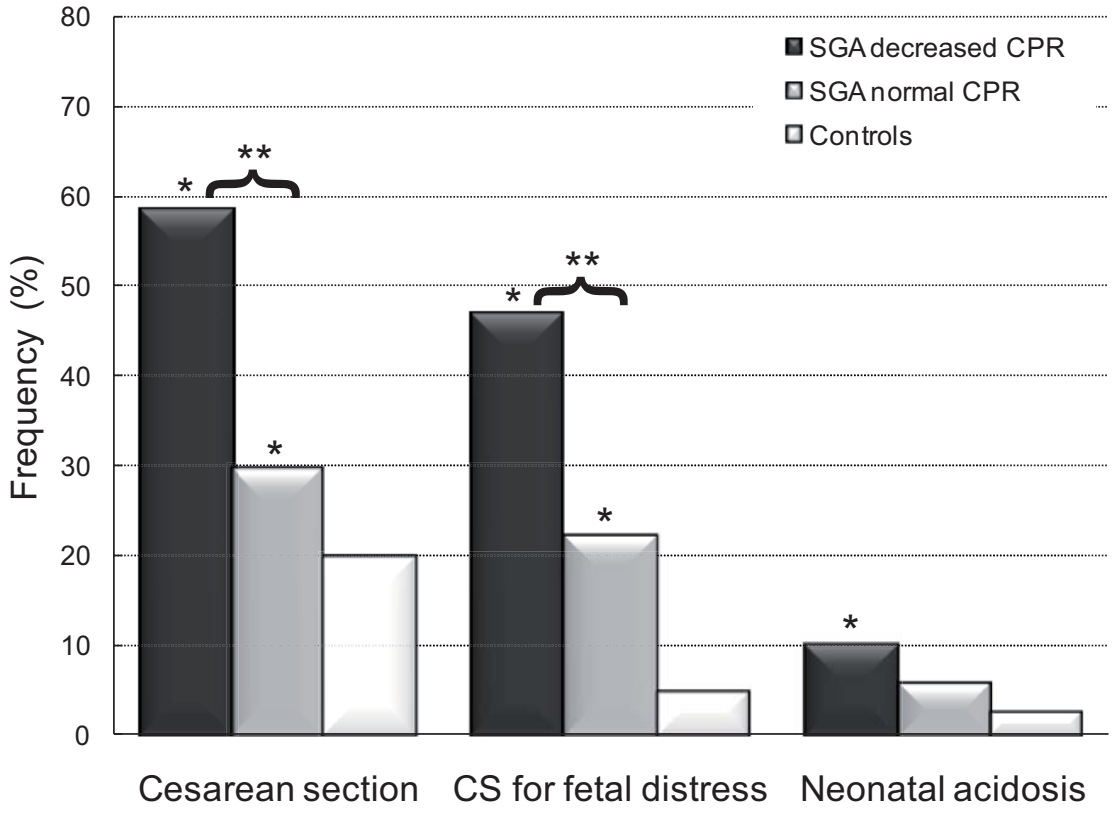
In 63% FD was diagnosed during the latent phase and in 37% during the first or second stage of labor. The proportion of SGA fetuses with increased FMBV, abnormal CPR and MCA vasodilation was 42.4%, 28.6%, and 14.8%, respectively.

The next figures show the frequency of intrapartum CS, CS due to FD and neonatal acidosis for controls and for SGA fetuses classified according to the presence or absence of brain sparing.

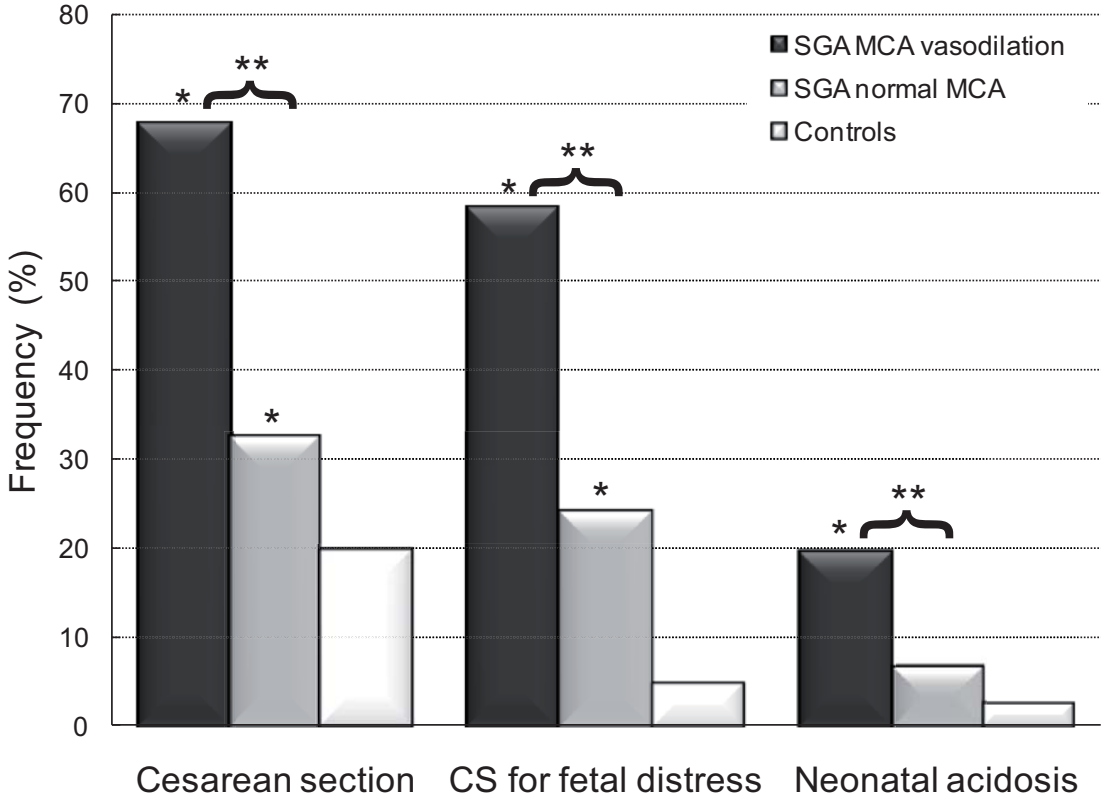
SGA fetuses with increased or normal FMBV had similar risks of intrapartum CS (41.6% vs. 34.7% respectively, p=0.31), emergency CS for FD (33.7% vs. 25.6% respectively, p=0.20) or neonatal acidosis (9.0% vs. 6.6% respectively, p=0.52).



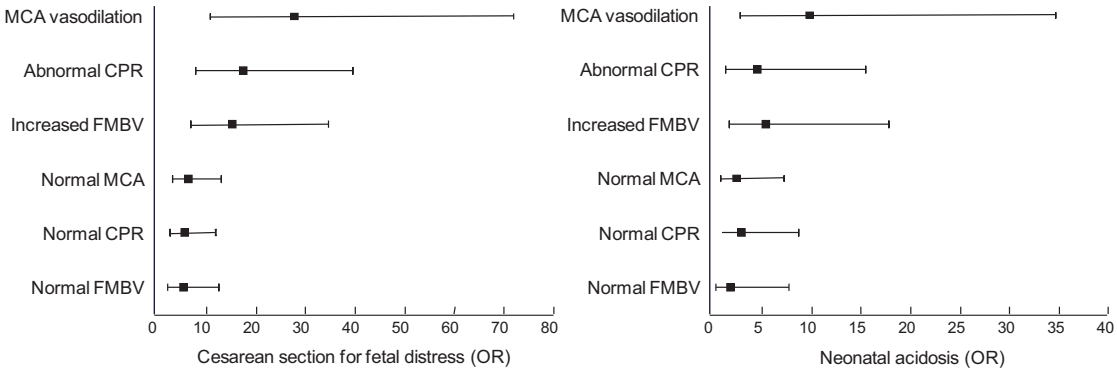
SGA fetuses with abnormal CPR had a significantly higher incidence of intrapartum CS than those with normal CPR (58.3% vs. 29.3% respectively, p<0.001) and higher rate of CS for FD (46.7% vs. 22.0% respectively, p<0.001) but were not significantly associated with the risk of neonatal acidosis (10.0% vs. 6.7% respectively, p=0.41).



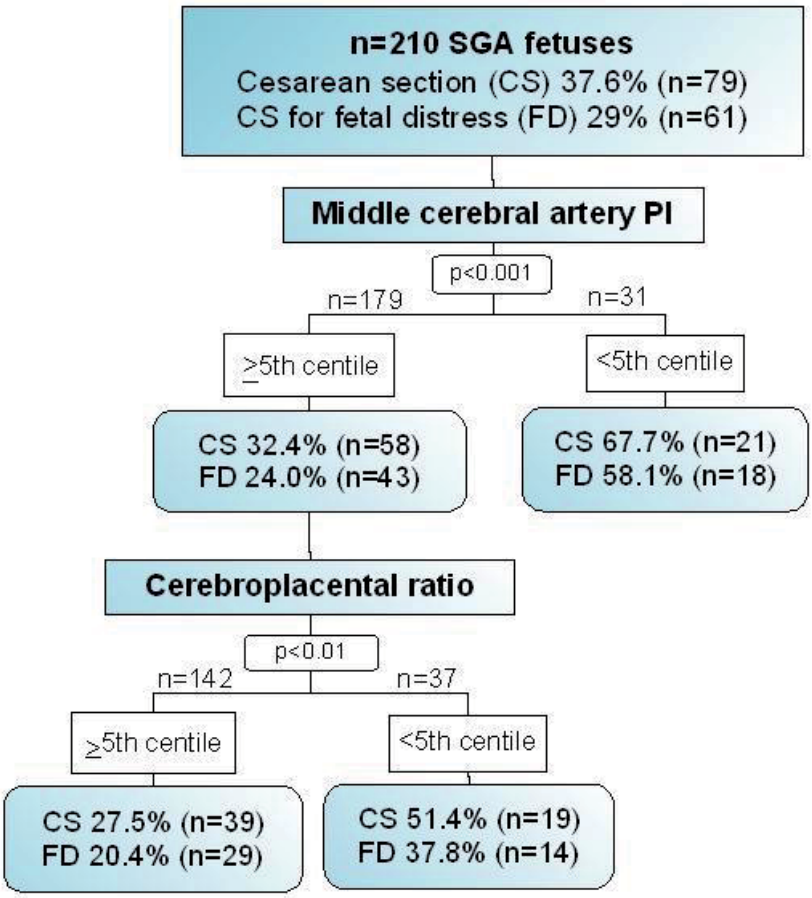
In addition, SGA fetuses with MCA vasodilation were associated with a significantly higher incidence of CS (67.7% vs. 32.4% in fetuses with normal MCA PI, p<0.001), CS for FD (58.1% vs. 24.0% respectively, p<0.001) and neonatal acidosis (19.4% vs. 5.6%, p<0.01).



This figure shows the odds ratio of emergency CS for FD and neonatal acidosis according to each brain Doppler parameter, with controls as the reference group.



The decision tree analysis profiled three groups with increasing risk of intrapartum CS and CS secondary to FD. MCA PI was the best initial predictor with a risk of 68% among SGA fetuses with MCA vasodilation. In the subgroup with normal MCA PI and a risk of 32%, evaluation of CPR allowed identification of cases with moderate (51.4%) and low risk (27.5%). The difference was explained by a significant increase in the rate of CS due to FD (58.1% in the group of MCA vasodilation, 37.8% in fetuses with normal MCA-abnormal CPR and 20.4% in fetuses with both normal parameters).



6.6 Project 6: Prediction of abnormal neonatal neurobehavior

The results of this project have been published in an international journal and have been presented at the 7th World Congress in Fetal Medicine, Fetal Medicine Foundation of London, 22-26 June 2008 in Sorrento, Italy; and at the 19th World Congress on Ultrasound in Obstetrics and Gynecology, 13-17 September 2009 in Hamburg, Germany. (oral communication: Cruz-Martinez R*, Figueras F, Oros D, Meler E, Padilla N, Hernandez-Andrade E, Gratacós E. Association between frontal tissue perfusion and neonatal neurobehavior in full-term small-for-gestational-age fetuses*) receiving the **"Young investigator award"** for the best oral communication for the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) (Ultrasound Obstet Gynecol January 2010; 35:126-132).

Study population

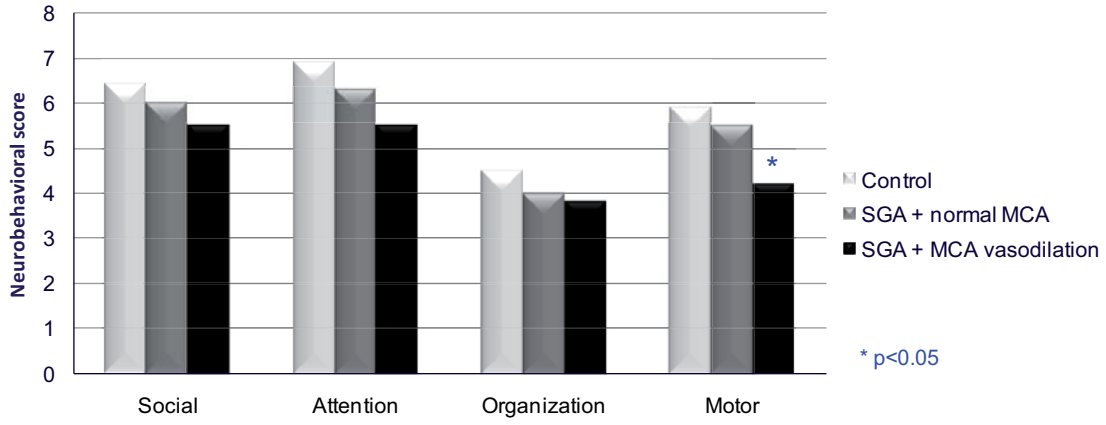
A total of 66 consecutive SGA cases were studied. In 6, frontal brain perfusion could not be evaluated due to the degree of engagement of the fetal head into the pelvis, leaving 60 cases for the analysis that were matched with 60 controls, resulting in a final population of 120 fetuses. In all cases, only the last Doppler examination within one week of delivery was included in the analysis.

This table shows the NBAS score by areas in the study groups. All neurobehavioral areas studied had significantly lower scores in the SGA group. The differences remained statistically significant after adjustment for potential confounders (maternal smoking, labor induction, mode of delivery, gestational age at delivery, gender and postnatal days at test performance).

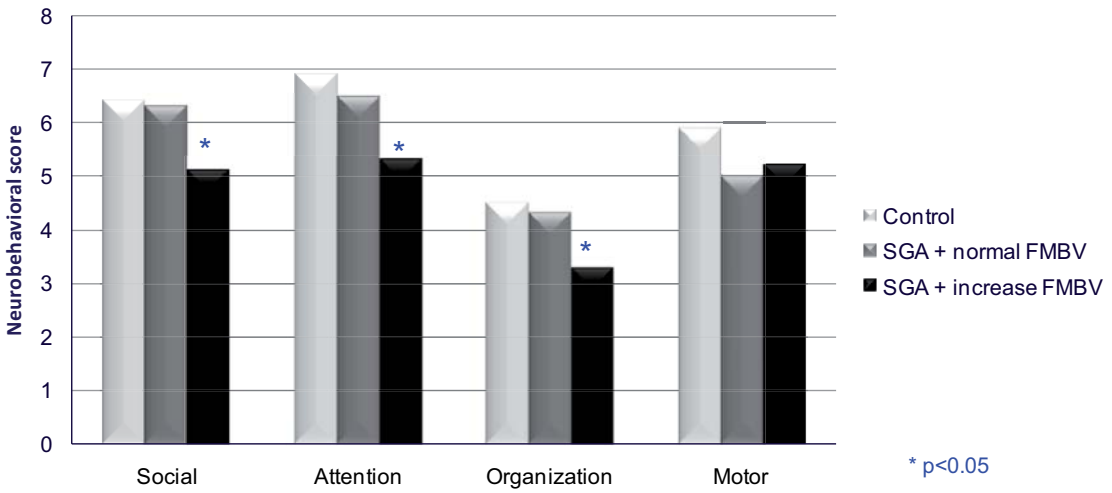
	AGA, *n*=60	**SGA**, *n*=60	p*	p**
Social-interactive	6.53 (1.3)	5.92 (1.7)	0.039	0.024
Attention capacity	6.83 (1.1)	6.10 (1.5)	0.006	0.003
Organization of state	4.67 (0.9)	4.07 (1.3)	0.010	0.029
Motor	5.77 (0.6)	5.46 (0.9)	0.047	0.031

The next figures show the NBAS score among SGA fetuses classified according to the presence or absence of MCA vasodilation and increased FMBV.

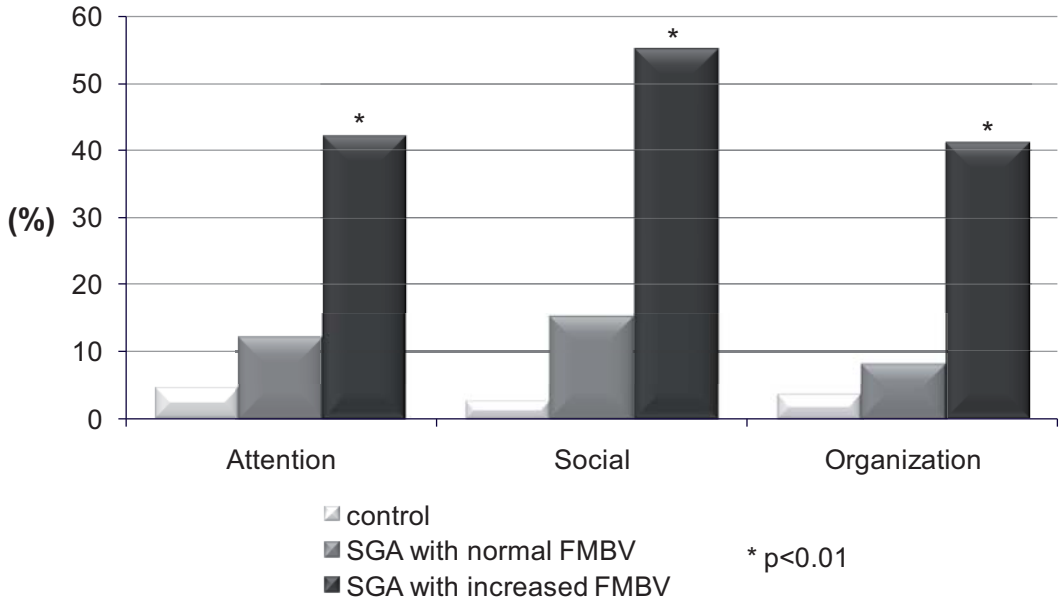
SGA cases with abnormal MCA PI showed significantly lower NBAS in the motor area with an adjusted odds ratio of (OR 8.99, 95% CI 1.39-58.21, p=0.021).



Among SGA fetuses, cases with increased FMBV showed significantly lower NBAS in social-interactive, attention and organization of state areas than the control group. In contrast, SGA fetuses with normal FMBV had NBAS values similar to controls.



Likewise, the frequency of abnormal neurobehavioral performance increased linearly and significantly when SGA fetuses were classified according to the presence of absence of increased frontal brain perfusion.



This table displays the odds ratios to present an abnormal NBAS score for SGA fetuses with and without increased perfusion.

	Normal FMBV (<p95)			Increased FMBV (>p95)		
Dependent variables	**OR**	**95% CI**	**p***	**OR**	**95% IC**	**p***
Social- interactive	1.20	0.11-13.31	0.882	7.82	1.32-46.53	0.024
Attention capacity	0	0	0.999	22.78	3.87-134.1	0.001
Organization of state	2.89	0.27-30.6	0.377	25.02	2.73-229.7	0.002
Motor	4.04	0.27-60.88	0.313	0.974	0.07-13.69	0.985

7. DISCUSSION

In the **first two studies** we provided normal references for brain tissue perfusion estimated by FMBV and left modified myocardial performance index and demonstrated that both parameters showed a significant progressive increase with advancing gestational age. The reference values here described provide physiological insights on the normal evolution of human brain and heart in pregnancy, and constituted the basis for the following 2 studies in the evaluation of fetal brain and cardiovascular parameters in term SGA fetuses.

The **third study** evaluated in near-term SGA fetuses, the temporal sequence of changes in brain tissue perfusion measured by FMVB in relation to other arterial spectral Doppler parameters. The study provides evidence that increased brain tissue perfusion occur earlier and in a higher proportion of cases than the CPR, MCA or ACA pulsed-Doppler abnormalities. These findings are consistent with previous studies regional brain perfusion in human fetuses with growth restriction, in which the onset of increased brain perfusion occurred long before a reduction in MCA PI below the 5th centile was reached(Hernandez-Andrade et al., 2008). We demonstrated that 40% of SGA fetuses present increased brain tissue perfusion. At 37 weeks brain redistribution was twice as frequent when assessed by FMBV as by MCA pulsed Doppler. This information is of clinical relevance since parameters offering earlier detection of brain redistribution could improve the detection of late-onset IUGR in a larger number of cases. These findings supported the following project evaluating the clinical impact of brain tissue perfusion in the monitoring of SGA fetuses.

In **study 4** we evaluate three different cardiac Doppler parameters and provided further evidence that a proportion of term SGA fetuses with normal UA Doppler show Doppler signs of cardiovascular adaptation/dysfunction in the form of an increased myocardial performance index and aortic isthmus impedance. Elevation in MPI was the most frequent abnormality with 28% of SGA fetuses showing abnormal values.

These findings are in line with previous studies in early-onset IUGR fetuses, where MPI becomes abnormal for early stages of fetal deterioration and before changes in DV and AoI could be observed (Cruz-Martinez et al., 2010).

Concerning the aortic isthmus, 15% of SGA with normal UA PI showed AoI abnormalities. Interestingly, 50% of these had reversed diastolic flow, which is normally regarded as a sign of advanced hypoxia(Makikallio et al., 2003). While previous studies have reported the presence of this sign in association with positive diastolic flow in the umbilical artery(Makikallio et al., 2002, Sonesson and Fouron, 1997), to our knowledge this study first demonstrates that AoI retrograde net blood flow may be observed in the presence of normal UA impedance. This observation further illustrates the poor performance of umbilical artery Doppler as a marker of risk in near term late-onset IUGR.

The proportion of cases with increased DV PI was similar to that of controls. This finding confirms the otherwise expected notion that DV Doppler provides no information in the identification of late-onset IUGR.

In the **5th study** we evaluated whether the combination of fetal brain Doppler parameters could improve the prediction of adverse perinatal outcome and demonstrate that abnormal brain Doppler before the onset of labor induction indentifies SGA fetuses at high risk of emergency cesarean section for fetal distress and neonatal acidosis. The data suggest that combination of MCA Doppler and CPR may refine prediction and establish subgroups with progressive risk of intrapartum fetal distress.

This study found that MCA Doppler had the highest value to predict the individual risk of emergency caesarean section for FD. The data are in line with Severi et al.(Severi et al., 2002) who reported that the risk of CS was increased in SGA fetuses with MCA vasodilation at the time of diagnosis. Concerning the CPR, decreased values had a higher sensitivity than MCA vasodilation for emergency CS for FD (45.9% vs. 29.5%), but lower specificity (78.5% vs. 91.3%). These findings are in agreement with previous studies in preterm

fetuses with growth restriction showing that CPR becomes abnormal earlier(Arbeille et al., 1995, Harrington et al., 1999, Turan et al., 2008) and thus, it has a greater sensitivity for adverse outcome than MCA(Gramellini et al., 1992, Habek et al., 2007, Jain et al., 2004, Odibo et al., 2005), but it is less specific(Bahado-Singh et al., 1999). As the decision tree algorithm illustrated, combining both MCA and CPR allowed an overall detection rate of the chances of fetal distress of 50% while maintaining a specificity of 76%.

Concerning brain tissue perfusion as measured by FMBV, this study showed no association with the risk of intrapartum FD or neonatal acidosis. As was demonstrated in project 2, brain tissue perfusion becomes abnormal earlier than spectral Doppler parameters such as MCA and CPR. It can be hypothesized that increased brain perfusion by FMBV identifies early stages of fetal hypoxia, when a majority of SGA fetuses are still capable of tolerating uterine contractions. On the contrary, abnormal MCA Doppler, which appears only in advanced stages(Oros et al., 2010), would indicate a lower fetal reserve in the presence of uterine contractions. In agreement with this contention, MCA was the only brain Doppler parameter associated with neonatal acidosis, which is a major contributor to neonatal neurological morbidity(Malin et al., 2010).

Finally, in **study 6** we assessed the impact of brain tissue perfusion as an early parameter of fetal hypoxia in improving the detection of abnormal neonatal neurobehavior and demonstrated that increased brain tissue perfusion is associated with a poorer neurobehavioral performance in the social-interactive organization, organization of state and attention capacity, indicating disrupted brain maturation with a better sensitivity than MCA Doppler, suggesting that this parameter could be used as a means to detect a larger proportion of late-onset IUGR with true hypoxia.

Concerning brain hemodynamics, there are no previous studies assessing the relationship between MCA Doppler and tissue perfusion with neonatal neurobehavior. In any event, our results are in line with long term follow up studies showing an association between MCA vasodilatation and suboptimal neurodevelopment in preterm (Scherjon et al., 2000, Kok et al., 2007) and term SGA fetuses (Eixarch et al., 2008). MCA vasodilatation was only associated with abnormal motor behavior, although there were no significant trends for most of the associations studied. It can therefore not be excluded that our study was underpowered to detect such associations. In any case, the findings support that frontal FMBV is a more sensitive parameter than MCA PI to identify increased brain perfusion and subtle degrees of neurological injury.

Strengths of these studies are the prospective design, the inclusion of a well-defined cohort of term SGA fetuses with normal UA Doppler exposed to labor induction, all Doppler parameters were weekly performed until one week of delivery and all abnormal values were confirmed in at least two consecutive examinations. In addition, obstetricians in charge of labor monitoring were blinded to the brain and cardiac Doppler parameters evaluated in this study.

Among the limitations of the studies, it must be acknowledged that brain Doppler evaluation may be difficult in advanced gestational ages and that it requires expertise which may be not readily available in certain settings. There are still limitations for the clinical application of tissue perfusion measurements in pregnancy. Firstly, estimation of brain tissue perfusion in the frontal lobe remains difficult in advanced gestational ages. Thus, while all the spectral cerebral and cardiovascular Doppler parameters could be examined in all cases independently of the fetal position, frontal perfusion could not be evaluated in a few cases with advanced gestational age. The sagittal view of the fetal head required to evaluate frontal lobe perfusion offers a good acoustic window with a clear observation of different structures of the fetal brain. However, at later gestational age, normally above 37 weeks, there is an intrinsic difficulty in

obtaining this plane correctly, mainly due to the posterior position and the degree of engagement of the fetal head into the pelvis in term fetuses. On contrary, in breech presentation or in preterm fetuses it is usually easily obtained. In addition, the clinical application is also limited because current ultrasound equipment does not yet incorporate FMBV algorithms for automatically tissue perfusion calculation. We recognize that time consumed in the offline image process to estimate FMBV is also a limitation (approximately 5 minutes by evaluated area).

As evidence suggesting intrauterine growth restriction as a potential risk factor of abnormal neurodevelopment and cardiovascular disease accumulates (Leitner et al., 2007, Barker et al., 1993, Crispi et al., 2010, Figueras et al., 2008, Figueras et al., 2009), early identification of late-onset IUGR may become a critical need for planning fetal surveillance, timely delivery, post-natal follow up and may prevent subsequent behavioral disruptions (Barnett, 1995, Yoshikawa, 1995, Kramer et al., 2008). If our findings are confirmed in further studies, and as commercial equipments incorporate automated methods to reliably estimate blood flow perfusion, the use of FMBV might gain acceptance to detect brain redistribution in SGA and eventually replace current methods based on spectral Doppler.

8. CONCLUSION

In summary, the results of this study add to the body of evidence demonstrating that fetuses classified in the diagnostic category of SGA include a proportion of cases that are in reality late-onset IUGR with mild forms of placental insufficiency not reflected in the umbilical artery Doppler.

The data provided by this support the notion that brain sparing is not an entirely protective mechanism and suggest a new clinical application for fetal brain Doppler in the selection of SGA fetuses with low and high risk of fetal distress during labor induction and abnormal neonatal neurobehavior. These findings support the assessment of brain Doppler in the monitoring of SGA fetuses to improve timely delivery and decision-making regarding induction of labor at term. In addition, our study also demonstrates the existence of cardiovascular Doppler abnormalities in term SGA fetuses. Future research on cardiovascular changes in mild forms of IUGR in combination with brain Doppler parameters might help to improve the detection of late-onset IUGR at risk of adverse perinatal outcome, abnormal neurodevelopment and postnatal cardiac dysfunction.

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10. ABBREVIATIONS

ACA	Anterior Cerebral Artery
AGA	Appropriated for Gestational Age
AoI	Aortic Isthmus
CN	Caudate Nucleus
CPR	Cerebroplacental Ratio
CS	Cesarean Section
DV	Ductus Venosus
ET	Ejection Time
FD	Fetal Distress
FMBV	Fractional Moving Blood Volume
GA	Gestational Age
ICT	Isovolumetric Contraction Time
ICV	Internal Cerebral Vein
IRT	Isovolumetric Relaxation Time
IUGR	Intrauterine Growth Restriction
MCA	Middle Cerebral Artery
MPI	Myocardial Performance Index
NBAS	Neonatal Behavioral Assessment Scale
PcA	Pericallosal Artery
PCA	Posterior Cerebral Artery
PI	Pulsatility Index
ROI	Region of interest
SD	Standard Deviation
SGA	Small for Gestational Age
SS	Sagittal Sinus
UA	Umbilical Artery