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ASSESSMENT OF MATERNAL AND FETAL DOPPLER IN LOW RISK TERM PREGNANCIES IN EARLY LABOUR AND CORRELATION WITH OBSTETRIC AND NEONATAL OUTCOME

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Abstract

The identification of intrapartum hypoxia is among the current challenges of the Obstetric practice. Available data have shown that such hypoxic events, despite being rare, most commonly occur in uneventful and apparently low risk pregnancies in appropriately grown fetuses.

The antenatal monitoring of fetal wellbeing aims to identify those fetuses at risk of hypoxic events related to labour and delivery and promptly arrange effective interventions in order to prevent adverse perinatal outcomes. Nevertheless, continuous intrapartum monitoring by means of cardiotocography (CTG) has not demonstrated a significant reduction in the incidence of adverse perinatal outcome and has been associated with an increase in the caesarean section rate, particularly among women considered at low risk.

Available evidences from the literature suggest that abnormalities in the uterine artery Doppler and in the ratio between fetal cerebral and umbilical Doppler (i.e. cerebroplacental ratio, CPR) are associated with conditions of subclinical placental function occurring in fetuses who have failed to achieve their growth potential, hence at risk of intrapartum complications. The purpose of this study is to prospectively assess maternal and fetal Doppler in early labour in order to evaluate whether abnormalities of the Doppler parameters may identify those fetuses at higher risk of intrapartum distress.

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Introduction

According to current estimates, over 20% of the 4 million neonatal deaths occurring every year in the world are related to labour complications (1,2). Intrapartum fetal hypoxia is among the leading causes of adverse perinatal outcomes such as death and hypoxic-ischemic encephalopathy leading to cerebral palsy and permanent disability (3-6). Additionally, up to one in two of hypoxic infants experience pulmonary complications (7) or other sequelae such as renal dysfunction secondary to acute kidney injury (7-9), cardiac complications and multiorgan dysfunction (10,11).

The aim of the intrapartum monitoring of the fetal wellbeing is to identify those fetuses experiencing hypoxic events which can lead to stillbirth and cerebral palsy or neurological impairment, in order to promptly set up effective interventions to prevent such adverse perinatal outcomes. The main tools for standard intrapartum fetal surveillance include the analysis of the fetal heart rate by means of cardiotocography (CTG) and intermittent auscultation. However, the evidence supporting their role in detecting the fetuses susceptible to intrapartum hypoxia is limited and strongly debated as such methods have not proven to result in an improvement of the perinatal outcomes (12-16). The CTG has poor characteristics as a test, with limited discriminatory power in identifying truly hypoxic fetuses. Moreover, the intra- and interobserver agreement is suboptimal and its

interpretation is subjective (17). Nonetheless, CTG still represents the mainstay for intrapartum fetal monitoring and is currently used in most delivery units (18,19).

According to the World Health Organization (WHO), protocols for midwifery-led care of labouring women with low risk pregnancy have been introduced worldwide with the purpose to provide "good health for the mother and the fetus with the lowest safely intervention level" (20). On this ground, a policy of labor surveillance by means of continuous CTG is recommended only in pregnancies with known risk factors for the mother and/or for the fetus, hence considered at risk of hypoxia. However, continuous CTG has shown low specificity in predicting fetal acidemia, has not been proven to decrease the incidence of perinatal mortality or cerebral palsy (13,19) and has been associated with a significant increase in the rate of caesarean section. Of note, when considering new technologies which have been implemented in order to support the "conventional" CTG interpretation (i.e. computerized analysis and ST-segment waveform analysis from the fetal electrocardiogram), available evidence has failed to demonstrate improvements in maternal or neonatal outcomes and a reduction of unnecessary obstetric intervention (20,21). On this basis, "continuous cardiotocography (CTG) is not recommended for the assessment of the fetal well-being in healthy pregnant women undergoing spontaneous labour" given its association with an increased rate of unnecessary caesarean section and other medical interventions and in the absence of evidence in terms of cost-effectiveness, acceptability and, most importantly, grade "A" evidence supporting its clinical role in improving birth outcomes (3,22). Therefore, one-to-one midwifery care and "intermittent auscultation of the fetal heart rate with either a Doppler ultrasound device or a Pinard fetal stethoscope" is

recommended in low risk women in the first and in the second stage of labour (23-26).

It is important to note, however, that most cases of labour hypoxia occur among apparently low risk pregnancies at term gestation (4,13). Therefore, such evidence suggests that the current triage strategy based on the medical history and the antepartum pregnancy characteristics does not allow the identification of those cases at risk for intrapartum hypoxia (27), hence unable to withstand the periods of intermittent hypoxia which characterize human labour.

Fetal growth and wellbeing is dependent on the maternal provision of oxygen and nutrients which are transferred by the placenta to the fetus in order to sustain its metabolic demand. In the majority of women, the placental function is sufficient to allow appropriate growth of the fetus throughout pregnancy and cope with the hypoxic stress of labour. Suboptimal placental function occurs when the utero-placental supply of substrates fails to fulfil the needs of the fetus and in most instances becomes evident as impaired fetal growth or fetal growth restriction (FGR), which is a major determinant of adverse perinatal outcomes including stillbirth (28-33).

From a pathophysiology point of view, fetal adaptation to chronic placental insufficiency and hypoxia leads to the preferential diversion of the fetal cardiac output in favour of the left ventricle, which then redirects the fetal blood flow to the brain and the heart (34-36). Such changes can be demonstrated and monitored using Doppler ultrasound. The evaluation of the placental function by umbilical artery (UA) Doppler has become a clinical standard to distinguish between SGA and FGR

fetuses (30,37-40) and should be the primary surveillance tool in the case of known fetal smallness (41). In a systematic review of 16 randomized controlled trials (RCT), including over 10,000 “high-risk” patients, the use of Doppler of the UA resulted in a variable decrease in the perinatal mortality (OR 0.71, 95% CI 0.52-0.98, 1.2 versus 1.7 percent, number needed to treat 203) (42). However, beyond 32 weeks UA Doppler is known to be within the normal range in most small fetuses and also in those defined as FGR due to impaired placental function (43-46). When considering only fetuses whose growth is considered “appropriate for the gestational age” (AGA), a systematic review of five RCTs and including over 14,000 low-risk or unselected patients found routine umbilical artery Doppler screening did not improve perinatal outcomes (47). Therefore, the use of UA Doppler is not recommended as a screening test or for the monitoring of the fetal wellbeing among low risk uneventful pregnancies (48-51).

The middle cerebral arteries (MCAs) are the two of the major branches of the circle of Willis carrying >80% of the cerebral circulation in the fetus and represent the most accessible cerebral vessels for antenatal ultrasound imaging (52,53). Under normal conditions the cerebral circulation is characterized by high resistance with continuous forward flow throughout the cardiac cycle (54,55). A reduction of the PI of the MCA identifies a process of adaptation by vasodilatation which is known as the “brain sparing effect” and has been associated with adverse fetal and perinatal outcome and suboptimal neurodevelopment at 2 years of age not only in early FGR showing an abnormal UA Doppler but also in late and term FGR fetuses with normal UA PI (46,56-58). The cerebroplacental ratio (CPR), also named as cerebro-umbilical (C-U) ratio, is considered an indicator of redistribution of the cardiac

output being accounted by the ratio between the UA PI and the MCA PI (28,29). The umbilico-cerebral (U-C) ratio represents an inverted ratio of the same parameters and is suggested to be a more accurate discriminator of cerebral redistribution compared to the CPR within the context of abnormal findings (59). This Doppler parameter, which was first described by Gramellini et al. in 1992 and proposed for the surveillance of the SGA fetuses in the third trimester (60), has been demonstrated to be more sensitive to hypoxia than its individual components on their own and to better correlate with adverse outcome in FGR as well as in SGA fetuses (60,61).

More recent evidence has suggested that the CPR may represent an early index of hitherto misdiagnosed fetal compromise also in the case of normal fetal growth and in pregnancies labelled as "low risk" (27,62,63). Indeed, depending on the gestational age at onset and on the extent of the placental dysfunction, the fetal growth may be within the normal range even though the fetus has failed to reach its growth potential, thus being at increased risk of adverse antenatal and perinatal outcomes. As a proof, when considering all cases of stillbirth at gestation close to term, at least two thirds of all cases occur in fetuses who are not small for their gestation (30,64-67). Over the last decade, several groups have demonstrated that even normally grown fetuses with reduced CPR beyond 36 weeks of gestation are at increased risk of perinatal complications, thus suggesting that a reduced CPR per se may represent a Doppler sign of subclinical, hence misdiagnosed, placental insufficiency precluding the fetus to reach its growth potential (30,46,68-71). Fetuses with a reduction in the CPR detected within 72 hours from labour onset have been reported to be at higher risk of stillbirth, obstetric intervention due to

intrapartum fetal distress, metabolic acidemia and neonatal morbidity, independently of their birthweight (63). Such findings were confirmed also by other research conducted on low risk pregnancies, thus leading to the hypothesis that the CPR can identify conditions of suboptimal placental function arising at late gestation and affecting the ability of the fetus to reach its growth potential albeit in the absence of fetal smallness (65,66,72-74). Nonetheless, the published data has shown a limited utility of the CPR in the prediction of adverse perinatal events, therefore caution has been advocated in incorporating this parameter into routine antenatal care within the context of low-risk pregnancies.

Similarly, to date there is no evidence supporting the evaluation of uterine artery (UtA) Doppler within the context of AGA fetuses in the third trimester. Uterine arteries are paired vessels undergoing major anatomic and functional adaptation during pregnancy as a result of the trophoblastic invasion of the maternal spiral arterioles – named as "remodelling" – in the first half of the gestation. Under normal conditions a sharp decrease in uterine artery (UtA) impedance to flow occurs as placental implantation progresses, which is reflected by the increased flow in diastole and disappearance of the notch present in the nonpregnant UtA (75,76). The "remodelling" of the spiral arteries is usually completed by 24 weeks, and indeed less prominent changes in UtA Doppler occur in the third trimester (77). Clinically, the UtA Doppler is commonly investigated to assess the severe early onset complications of impaired placentation. A systematic review and meta-analysis demonstrated the role of UtA Doppler ultrasonography as a predictor of FGR, particularly when performed in the second trimester and particularly for early FGR (78). UtA Doppler has not been incorporated in the recently published

diagnostic criteria for late FGR (30), however other research groups on late FGR have suggested its role for the longitudinal monitoring and management of SGA/late FGR fetuses (79,80), abnormal findings being associated with an increased risk of adverse perinatal events (81,82). This supports the concept that abnormally raised UtA PI in the third trimester may help in discriminating between SGA and late FGR (68,69,83). In this context, MacDonald et al. described the cerebral-placental-uterine ratio (CPUR) as a novel marker for discriminating SGA from FGR fetuses which is accounted by the ratio between the CPR and the UtA PI (84). As regards AGA fetuses, to date only a retrospective study evaluating the incidence of stillbirth within a population of apparently appropriately grown fetuses in the third trimester has demonstrated an association between raised UtA PI and adverse perinatal outcome (85).

When considering all cases of fetal hypoxia, 75% occur during labour as a result of uterine contractions. Labour is the most challenging time span for feto-placental unit being uterine contractions associated with up to 60% of the decline in uterine artery flow velocity (66). The majority of appropriately grown, healthy, term fetuses are able to withstand the reduction of the uterine perfusion over a prolonged period of time, mainly because of their high myocardial glycogen stores, the increased oxygen affinity of HbF and the autonomic fetal defensive mechanisms against the hypoxic injuries (86-90). On the other hand, inadequate placental function is associated with the progressive development of fetal acidosis due to an inability to correct the impaired gas exchange between contractions (91,92). On this ground, it is reasonable to hypothesize that undiagnosed conditions of impaired placental function could be unmasked by uterine contractions and that the

evaluation of the CPR and the UtA Doppler in early labour may be useful for the identification of a subgroup of low risk women at higher risk of perinatal complications. The aim of this prospective observational study is to investigate whether the fetal and the maternal Doppler can predict the occurrence emergency delivery due to intrapartum fetal distress and the occurrence of adverse perinatal outcome among uneventful term pregnancies in early stages of spontaneous labour. Moreover, this study aims to assess if maternal-fetal Doppler velocimetry is capable to improve the detection of those cases who are more likely to require continuous CTG monitoring and those in which intermittent CTG is the best choice.

Methods

This was a prospective, multicenter, observational study involving four European Tertiary Academic centres (Universities of Parma and Rome Tor Vergata, Italy; Imperial College London, United Kingdom; University of Barcelona, Spain) and conducted between January 1st, 2016 and September 30th, 2019.

All women with singleton pregnancy were approached on admission for early spontaneous labor, which was defined by means of a fully effaced, 3-4 cm dilatated cervix coupled with at least 3 contractions in 10 minutes recorded at tocography (93,94). At recruitment, all women were at term pregnancy, which was defined by a gestational age between 37^{+0} and 41^{+6} weeks. This was determined either by the last menstrual period or by the crown-rump length measurement performed in the first trimester, according to the National guidelines of the participating Centres (95-97).

As per the design of the study, prerequisites for study enrolment were represented by the presence of a cephalic presenting fetus and a normal admission CTG according to the classification by the International Federation of Gynecology and Obstetrics (FIGO) (98). Additionally, all the included fetuses were identified as "low risk" on the basis of individual chart review and fetal growth was considered appropriate based on a growth scan performed between 30 and 36 weeks or on the clinical assessment of the symphysis-fundal height at 36 to 37 weeks. Despite being defined as "low risk", all the enrolled patients were submitted to continuous CTG during labor as per policy of the three Centres involved in this study. In all the included cases delivery occurred within 24 hours from recruitment.

Exclusion criteria were represented by one or more of the following: active phase of the first stage of labor with cervical dilatation ≥5 cm, multiple pregnancy, preexisting chronic maternal medical disorders or poor obstetric history, any complication diagnosed during the index pregnancy, including hypertensive disorders and gestational diabetes, morbid obesity at booking as defined by body mass index (BMI) ≥40 kg/m^2, previously identified fetal growth restriction, fetal anomalies, aneuploidies and genetic syndromes either antenatally known or postnatally diagnosed, evidence of intrauterine infection, antepartum haemorrhage, premature rupture of the membranes for ≥18 hours, scarred uterus as per previous caesarean section (CS) or fibroid removal and age below 18 years.

In each of the participating Centres, Doppler recordings of the umbilical artery (UA), the middle cerebral artery (MCA) and the left and the right uterine artery (UtA) were undertaken by trained practitioners and the pulsatility index (PI) of all the parameters was measured. All Doppler recordings were performed in between uterine contractions as ensured by tocography and uterine palpation with the patient lying in a semirecumbent position. Doppler parameters were measured according to the recommendations by the International Society on Ultrasound in Obstetrics and Gynecology (52), i.e. using an angle of insonation below 30 degrees, in the absence of maternal and fetal movements and using an automated trace of at least 3 consecutive waveforms. In all cases fetal Doppler findings were obtained before epidural analgesia.

The UA PI and the MCA PI were converted into multiples of the median (MoMs) based on formerly reported reference ranges (99) in order to adjust for the gestational age at study recruitment. The UA PI MoM value that selected the

highest 5% of the cases was chosen as the 95th centile and increased UA PI MoM was defined based on UA PI MoM within the highest 5 percentiles of the study population. Similarly, the MCA PI MoM value that selected the lowest 5% of the enrolled women was chosen as the 5th centile and reduced MCA PI MoM was defined based on MCA PI MoM within the lowest 5 percentiles of the study population.

The CPR values were computed by dividing the MCA PI and the UA PI and converted into multiples of the median (MoM) based on formerly reported reference ranges (100), thus correcting for gestational age as previously described (65). The CPR MoM value that selected the lowest 10% of the cases was chosen as the 10th centile and reduced CPR MoM was defined based on CPR MoM within the lowest decile of the included population.

The mean UtA PI was computed as the mean of the PI of the left UtA and of the right UtA PI and converted into MoMs based on formerly reported reference ranges (101), thus correcting for gestational age. The mean UtA PI MoM value that selected the highest 5% of the cases was chosen as the 95th centile and increased mean UtA PI MoM was defined based on mean UtA PI MoM within the highest 5 percentiles of the included population.

In the absence of previously reported data reporting the reference ranges across gestation, the CPUR was calculated by dividing the CPR MoM and the UtA PI MoM. The CPUR value that selected the lowest 10% of the cases was chosen as the 10th centile and reduced CPUR was defined based on CPUR within the lowest decile of the included population.

Information concerning maternal age, ethnicity, parity, gestation at the onset of labor and body mass index (BMI) at booking and at delivery were recorded.

The clinicians responsible for the intrapartum care and the patients themselves were blinded to the US findings.

After delivery, intrapartum and neonatal outcome data were collected from patient case notes. The primary outcome of the study was to evaluate the relationship between the CPR and the mean UtA PI measured in early labour and the need to expedite delivery due to intrapartum fetal distress. Deliveries were categorized according to the mode of delivery in spontaneous vaginal delivery (SVD), obstetric intervention (OI), OI secondary to dystocia (OI dystocia) and OI secondary to fetal distress (OI distress). Secondary outcomes were represented by adverse perinatal events, which included low APGAR score at 5 minutes, abnormal cord gases either in terms of low cord arterial pH or increased cord arterial base excess (BE), delivery of a small-for-gestational age (SGA) neonate, transfer to Neonatal Intensive Care Unit (NICU), hypoxic-ischemic encephalopathy, stillbirth/neonatal death and composite adverse perinatal outcome.

The diagnosis of intrapartum fetal distress was subjectively defined by the physician in charge for the patient care based on abnormal CTG tracing according to FIGO classification system (98). In order to ensure consistency within Tertiary-Unit settings, in all the participating Centres CTG tracings are routinely reviewed by two senior members of the obstetric team before expediting delivery due to intrapartum fetal distress. As per common policy of the participating Centres, the analysis of the cord gases was performed according to the recommendations by the

American College of Obstetricians and Gynecologysts (102) and in all other cases of obstetric intervention. Paired umbilical cord gases were routinely obtained either within 60 seconds from birth or from double-clamped cord segments and a prerequisite for study inclusion was the availability of the result of either the cord arterial or venous pH and base excess. Abnormal cord gases were diagnosed in the case of either umbilical artery cord pH <7.10 or umbilical artery BE >12.

Neonatal outcome was assessed by examining birthweight and birthweight centile corrected for gender (103), cord arterial pH and base excess at delivery, Apgar score at 1 and 5 minutes, need for resuscitation at birth and admission to NICU. Adverse perinatal outcome was scored as previously described (18): 1) Apgar >7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH >7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) BE <8 = 0, > 8 and <12 = 1, >12 = 2; 4) NICU admission or need for resuscitation at birth No = 0, Yes = 1. Composite adverse perinatal outcome (CAO) was defined by a score >3. SGA neonates were identified as those weighting <10th percentile for the given gestational age corrected for gender and parity according to the Italian growth charts published by Bertino et al. (103).

At the time of the study design no data on the association between the CPR in early labor and the mode of delivery in uncomplicated pregnancies was available, however a sample size calculation was attempted as follows. The patients eligible for our study belong to the categories 1 and 3 according to the classification described by Robson et al. (104). In 2015, 817 and 610 patients who delivered at the University Hospital of Parma belonged to the Categories 1 and 3, respectively, and accounted for 54.4% of all deliveries (1427/2623). The CS rate was 11% (89 patients) for Category 1 and 3.4% (21 patients) for Category 3 averaging at 7.7%

in the overall target population. Previously published data on low risk not laboring women showed that in low risk fetuses with CPR below the 10th percentile the CS rate due to fetal distress was nearly four times higher (36.4% vs 9.5%) than among fetuses with CPR between 10th and 90th percentile for gestational age. In the same study, the percentage of CS due to fetal distress was 42.2% (73). We applied these percentages to the local population of the University Hospital of Parma and estimated that the number of low risk patients needed to demonstrate that a reduced CPR in early labor is associated with a four-times higher rate of cesarean section rate due to fetal distress (from 3.2% to 12.8%) in order to obtain statistical power of 80% ($p < 0.05$) would have been 288.

In the absence of prospective and retrospective on the role of UtA Doppler in low risk pregnancy at term, no sample size calculation was attempted to test the association between mean UtA PI and the primary outcome of the study at the time of the study design. Nonetheless, an interim analysis of the study dataset showing an incidence of OI due to fetal distress of 13.0% in cases with increased mean UtA PI MoM vs 7.6% in mothers with mean UtA PI MoM below the 95th percentile allowed to estimate that the number of low risk patients needed to demonstrate that a raised UtA PI in early labor is associated with an almost twice higher rate of cesarean section due to fetal distress would have been 992.

Ethics approval for this study was granted by the local Ethics Committee in all the involved centers and all the eligible patients signed a consent form before study enrollment. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Inc., Armonk, NY, USA). Normal or abnormal distribution of continuous variables was preliminary evaluated by means of the

Kolmogorov-Smirnov and the Shapiro-Wilk tests and data were shown as mean ± standard deviation or as median (range) accordingly. Comparison of normally and non-normally distributed continuous variables included the T test for independent sample or the ANOVA test and the Mann-Whitney U-test or the Kruskal-Wallis test, respectively. Categorical variables were reported as number (percentage) and compared using the Chi-square test.

Logistic regression analysis was used to control for potential confounding variables, while the prediction performance of the evaluated Doppler parameters for OI due to intrapartum fetal distress was determined by receiver operating characteristic (ROC) curve analysis. The method of DeLong et al. was used for the comparison of the ROC curves (105). $p < 0.05$ was considered as statistically significant.

Results

Overall, 804 women were recruited over the study period, of whom 455 were recruited by a single dedicated investigator (AD) at the University Hospital of Parma and at Queen Charlotte's and Chelsea Hospital (Imperial College London), while 166 and 183 cases were provided by the University of Barcelona and Rome Tor Vergata, respectively.

Demographic features, intrapartum parameters and labour outcomes of the included cases are summarized in Table 1. The UA PI MoM, the MCA PI MoM, the CPR MoM, the mean UtA PI MoM and the CPUR were all normally distributed throughout the study population.

SVD occurred in 659 women (82.0%), while CS and ID were recorded in 88 (10.9%) and 57 (7.1%) cases, respectively. Overall, OI due to fetal distress was performed in 54 (6.7%) women, which included 25 CSs (3.1%) and 29 IDs (3.6%). No case of hypoxic-ischemic encephalopathy and stillbirth or neonatal death was recorded (Table 1). The demographic characteristics and the intrapartum and perinatal outcomes in cases with normal vs abnormal (either reduced or increased) UA PI MoM, MCA PI MoM, CPR MoM, mean UtA PI MoM and CPUR are shown in Tables 2-6.

Increased UA PI MoM was defined as UA PI MoM >1.45 and recorded in 41 women. Cases with increased UA PI MoM showed higher booking BMI (27.7±4.0 vs 23.9±4.1, p<0.001), BMI at term (31.2±6.8 vs 28.3±4.2, p<0.001) and gestational age at delivery ($40^{+1}\pm0^{+6}$ vs $39^{+6}\pm1^{+1}$, p=0.03), higher incidence of oxytocin augmentation (68.3% vs 50.2%, p=0.02) and epidural in labour (75.6% vs

58.2%, p=0.03) and median Apgar at 1 minute (9 (7-10) vs 9 (1-10), p<0.001), while the frequency of pH <7.20 was lower (9.8% vs 25.5%, p=0.02) compared to cases with normal UA PI MoM (Table 2).

Reduced MCA PI MoM was identified by a MCA PI MoM <0.67 and accounted for 37 women. The MCA PI below the 5th percentile was associated with an earlier gestational age at delivery ($38^{+6}\pm1^{+0}$ vs $39^{+6}\pm1^{+1}$, p<0.001), an over two-fold higher the incidence of OI due to intrapartum distress (18.2% vs 7.1%, p=0.02) and also the frequency of cord arterial pH <7.00 and cord arterial BE >12 was higher compared to cases with normal MCA PI MoM (6.1% vs 0.2%, p<0.001 and 12.5% vs 3.0%, p=0.004, respectively) (Table 3).

A cut-off threshold of CPR MoM of 0.62 was used to define a reduced CPR MoM, which occurred in 75 women. Women with CPR MoM within the lowest decile of the study population delivered at earlier gestation ($39^{+2}\pm1^{+0}$ vs $39^{+6}\pm1^{+1}$ weeks, p<0.001) and showed an over seven-fold higher incidence of OI due to fetal distress (30.7% vs 4.3%, p<0.001). Moreover, lower median 5 minutes Apgar score (9 (7-10) vs 9 (7-10), p=0.04) and cord arterial pH (7.22±0.10 vs 7.26±0.09, p<0.001) were recorded in women with reduced CPR MoM, while the mean cord arterial base excess (6.64±3.30 vs 5.70±2.89, p=0.01) and the incidence of oxytocin augmentation (65.3% vs 49.7%, p=0.01), epidural in labour (73.3% vs 57.6%, p=0.008), Apgar score <7 at 1 minute (8.0% vs 1.8%, p=0.01), cord arterial pH <7.20 (37.7% vs 23.2%, p=0.008), <7.10 (11.6% vs 2.1%, p<0.001) and <7.00 (2.9% vs 0.2%, p=0.001), NICU admission (6.7% vs 1.0%, p<0.001) and composite adverse perinatal outcome (13.3% vs 3.0%, p<0.001) were higher in women with CPR MoM <10th percentile compared to those with normal CPR MoM (Table 4).

Increased mean UtA PI MoM was defined as mean UtA PI MoM >1.66, which was recorded in 40 cases. Women with mean UtA PI >95th percentile of the study population showed lower birthweight (3171±427 vs 3385±421 grams, p=0.002) and birthweight percentile (37.1±28.1 vs 50.6±28.5, p=0.004) compared to cases with normal mean UtA PI MoM. Furthermore, increased mean UtA PI was associated with a lower rate of epidural in labour (42.5% vs 59.9%, p=0.03) and a higher incidence of SGA neonates (20.0% vs 6.7%, p=0.002), cord arterial BE >12 (10.8% vs 3.0%, p=0.01) and NICU admission or need for resuscitation at birth (7.5% vs 1.2%, p=0.001)(Table 5). There was a linear relationship between UtA PI MoM and the CPR MoM as the increase of the mean UtA PI MoM was correlated to a reduction of the CPR MoM (correlation coefficient -0.159, p>0.001).

A reduced CPUR was identified by a cut-off threshold of 0.49, which occurred in 75 women. In cases showing CPUR <10th percentile for the study population, a lower gestational age at delivery ($39^{+3}\pm1^{+0}$ vs $39^{+6}\pm1^{+1}$, p=0.005), cord arterial pH (7.23±0.11 vs 7.26±0.09, p=0.02) and birthweight (3251±431 vs 3387±422 grams, p=0.008) were recorded. Conversely, the cord arterial BE was higher (6.72±3.62 vs 5.68±2.84, p=0.005) and the incidence of Apgar <7 at 1 minute (8.0% vs 1.8%, p=0.001), cord arterial pH <7.10 (10.0% vs 2.2%, p<0.001), cord arterial BE >8 (27.5% vs 17.5%, p=0.04) and >12 (13.0% vs 2.3%, p<0.001), NICU admission or need for resuscitation at birth (5.3% vs 1.1%, p=0.004) and composite adverse outcome (13.3% vs 3.0%, p<0.001) was also higher in women with reduced CPUR compared to those with normal CPUR (Table 6).

Primary outcome: relationship between maternal and fetal Doppler in early labour and obstetric intervention due to intrapartum fetal distress

Maternal demographics, the distribution of Doppler values and intrapartum and neonatal outcomes according to the mode of delivery are shown in Table 7. Within our population of low risk pregnancies at term gestation submitted to maternal and fetal Doppler evaluation in early labour, all the evaluated Doppler parameters were associated with the primary outcome being UA PI MoM and mean UtA PI MoM higher and MCA PI MoM, CPR MoM and CPUR lower in women who underwent OI due to intrapartum fetal distress. When evaluating the baseline risk for OI due to intrapartum fetal distress by means of logistic regression analysis and a model including antepartum and intrapartum characteristics such as maternal age, booking BMI, ethnicity, parity, smoking status, oxytocin augmentation and epidural in labour, the UA PI MoM (5.202, 95%CI (1.299-20.833), p=0.02), the MCA PI MoM (14.037, 95% CI (2.705-72.835), p=0.002), the CPR MoM (65.939, 95% CI (13.562-320.603), p<0.001), the mean UtA PI MoM (3.204, 95%CI (1.399-7.337), p=0.006) and the CPUR (OR 16.055, 95% CI (4.744-54.342), p<0.001) all were independently associated with OI due to intrapartum fetal distress, as were the MCA PI MoM <5th percentile (OR 1.267, 95%CI (1.048-1.532), p=0.02), the CPR MoM <10th percentile (OR 1.270, 95%CI (1.189-1.356), p<0.001), the mean UtA PI MoM >95th percentile (OR 1.012, 95%CI (1.002-1.022), p=0.02) and the CPUR <10th percentile (OR 1.243, 95%CI (1.165-1.327), p<0.001).

At ROC curve analysis the area under the curve (AUC) for the identification of OI due intrapartum fetal distress according to the baseline risk model was 0.619, 95%CI (0.540-0,699), p=0.004. The comparison between the AUC of the baseline

risk model with that of models including the baseline risk and the evaluated Doppler parameters showed an increased AUC for the models including the MCA PI MoM (AUC 0.685, 95%CI (0.610-0.760), p<0.001), the CPR MoM (AUC 0.748, 95%CI (0.678-0.818), p<0.001), the CPUR (AUC 0.725, 95%CI (0.651-0.798), p<0.001), the CPR MoM <10th percentile (AUC 0.768, 95%CI (0.697-0.840), p<0.001) and the CPUR <10th percentile (AUC 0.757, 95%CI (0.685-0.829), p<0.001) compared to the baseline risk (p=0.04, p=0.008, p=0.04, p<0.001 and p<0.001, respectively). No difference in the AUC was noted across the models including the baseline risk and the different Doppler parameters (MCA PI MoM vs CPR MoM, p=0.08; MCA PI MoM vs CPUR, p=0.35; MCA PI MoM vs CPUR <10th percentile p; CPR MoM vs CPUR, p=0.38; CPR MoM vs CPR MoM <10th percentile, p=0.54; CPR MoM vs CPUR <10th percentile, p=0.80; CPUR vs CPR MoM <10th percentile, p=0.25; CPUR vs CPUR MoM <10th percentile, p=0.37; CPR MoM <10th percentile vs CPUR <10th percentile, p=0.66), with the only exception of the comparison between the model including MCA PI MoM and that with CPR MoM <10th percentile (p=0.02), which was the Doppler parameter associated with the highest AUC. When evaluating additional models including maternal and fetal Doppler (i.e. the UtA Doppler and the CPR, respectively), the highest AUC for of OI due to intrapartum fetal distress was obtained by combining the CPR MoM <10th percentile and the mean UtA PI MoM >95th percentile, which yielded an AUC 0.783, 95%CI (0.712-0.855), p<0.001. However, no difference was noted at paired comparison of this latter AUC with that of the models including the CPR MoM <10th percentile only (p=0.31) nor the combination or either CPR MoM <10th percentile or mean UtA PI MoM >95th percentile (AUC 0.775, 95%CI (0.705-0.845), p<0.001)(p=0.42). Conversely, the combined model including the CPR

MoM <10th percentile and the mean UtA PI MoM >95th percentile showed a higher AUC compared to that of the model including CPR MoM <10th percentile and mean UtA PI MoM >95th percentile (AUC 0.658, 95%CI (0.576-0.739), p<0.001)(p=0.002)(Figure 1). CPR MoM and mean UtA PI MoM were both abnormal (i.e. CPR MoM <10th percentile and mean UtA PI MoM >95th percentile) in 6 (0.7%) cases and both within the normal range in 695 (86.4%) cases, while abnormal CPR MoM and abnormal mean UtA PI MoM were recorded in 69 (8.6%) and 34 (4.2%) women, respectively. Of note, OI due to intrapartum fetal distress was performed in 4/6 cases (66.7%) showing CPR MoM <10th percentile and mean UtA PI MoM >95th percentile.

The sensitivity, the specificity, the positive and the negative predictive value (PPV and NPV, respectively) and the positive and the negative likelihood ratios (LR+ and LR-, respectively) for OI due to intrapartum fetal distress in cases with CPR MoM <10th percentile, in cases with CPR MoM <10th percentile and/or mean uterine artery (UtA) pulsatility index (PI) MoM >95th percentile, for the models obtained by combining the baseline characteristics with the CPR MoM <10th percentile, the CPR MoM <10th percentile and/or the mean uterine artery (UtA) pulsatility index (PI) MoM >95th percentile and for the combined model including the CPR MoM <10th percentile and the mean UtA PI MoM >95th percentile is shown in Table 8. Overall, the maternal and fetal Doppler assessment in early labour proved to be a poor predictor of OI due to intrapartum fetal distress being the all the models associated with a sensitivity on or below the 78% and a with a low PPV.

Secondary outcomes

With regards to the secondary outcomes of the study, there was no case of Apgar <7 at 5 minutes. Cord arterial pH <7.10 and cord arterial base excess >12 were recorded in 21/699 (3.0%) and 23/673 (3.4%) cases, respectively, while abnormal cord gases, birthweight <10th centile for the gestational age, transfer to NICU or need to resuscitation at birth and composite adverse perinatal outcome were recorded in 38/731 (5.2%), 59 (7.3%), 12 (1.5%) and 32 (4.0%) women, respectively. Given the low incidence of adverse outcome within our low risk population, the maternal demographics, the distribution of Doppler values and the intrapartum outcomes were analyzed according to the occurrence of abnormal cord gases and composite adverse perinatal outcome and the postnatal diagnosis of SGA.

When investigating the relationship between abnormal cord gases and Doppler findings in early labour, the MCA PI MoM (0.90±0.19 vs 0.97±0.21, p 0.045) and the mean UtA PI MoM (1.26±0.30 vs 1.12±0.29, p 0.004) differed between cases with and without abnormal umbilical artery pH or BE at birth (Table 9), however only the mean UtA PI MoM proved to be independently associated with abnormal cord gases at logistic regression analysis (OR 3.550, 95%CI (1.327-9.497), p=0.01). At ROC curve analysis, the incorporation of the mean UtA PI MoM (AUC 0.800, 95%CI (0.768-0.828), p<0.001) into a model including the baseline maternal caracteristics and the intrapartum parameters (AUC 0.768, 95%CI (0.736-0.799), p<0.001) yielded an impovement in the identification of the cases with abnormal arterial cord gases at birth (p=0.04) (Figure 2) and was associated with a sensitivity of 0.73, 95%CI (0.56-0.86), a specificity of 0.72, 95%CI (0.66-0.75), a PPV of 0.12,

95%CI (0.08-0.17), a NPV of 0.98, 95%CI (0.96-0.99), a LR+ of 2.57, 95% CI (2.04-3.23) and a LR- of 2.65, 95% CI (1.56-4.51).

As regards the relationship between CAO and Doppler recordings in early labour, higher mean UtA PI MoM (1.24±0.32 vs 1.11±0.29, p=0.02) and lower MCA PI MoM (0.88±0.17 vs 0.98±0.21, p=0.01) and CPUR (0.69±0.24 vs 0.92±0.40, p=0.04) were recorded in cases experiencing adverse outcome (Table 10). At logistic regression analysis both the MCA PI MoM and the mean UtA PI MoM proved to be independently associated with CAO (OR 11.320, 95%CI (1.377-93.080), p=0.02 and OR 3.048, 95%CI (1.082-8.586), p=0.03, respectively). At ROC curve analysis no difference was found between the models including MCA PI MoM (AUC 0.785, 95%CI (0.754-0.813), p<0.001), the mean UtA PI MoM (AUC 0.775, 95%CI (0.744-0.804), p<0.001) and the combination of MCA PI MoM and mean UtA PI MoM (AUC 0.805, 95%CI (0.745-0.865), p<0.001)(p=0.63 for the model including MCA PI MoM vs model including mean UtA PI MoM; p=0.19 for the model including MCA PI MoM vs model combining MCA PI MoM and mean UtA PI MoM; p=0.16 for the model including mean UtA PI MoM vs model combining MCA PI MoM and mean UtA PI MoM). The model combining the MCA PI MoM and the mean UtA PI MoM was associated with the highest accuracy in the identification of CAO (Figure 3) yielding a sensitivity of 0.68, 95%CI (0.49-0.83), a specificity of 0.79, 95%CI (0.76-0.82), a PPV of 0.12, 95%CI (0.07-0.17), a NPV of 0.98, 95%CI (0.97-0.99), a LR+ of 3.23, 95%CI (2.44-4.28) and a LR- of 2.45, 95%CI (1.47-4.09).

The postnatal diagnosis of SGA was associated with a higher UA PI MoM (1.21±0.18 vs 1.05±0.21, p<0.001) and mean UtA PI MoM (1.25±0.39 vs

1.11±0.28, p<0.001) and lower CPR MoM (0.80±0.16 vs 0.95±0.29, p<0.001) and CPUR (0.69±0.24 vs 0.92±0.40, p<0.001) (Table 11). At logistic regression analysis, which included maternal age, booking and term pregnancy BMI, smoking status, ethnicity and parity, the UA PI MoM (OR 31.163, 95%CI (7.984-121.626), p<0.001), the CPR MoM (OR 10.223, 95%CI (2.860-36.542), p<0.001), the mean UtA PI MoM (OR 3.489, 95%CI (1.576-7.723), p=0.002), the CPUR MoM (OR 8.435, 95%CI (2.917-24.397), p<0.001) and the UtA PI MoM >95th percentile (OR 1.011, 95%CI (1.001-1.021), p=0.03) were all independently associated with the postnatal diagnosis of SGA. At ROC curve analysis (Figure 4) the comparison of the baseline AUC for SGA (AUC 0.619, 95%CI (0.546-0.692), p=0.003) with that of the models including the baseline characteristics and the Doppler parameters showed a higher AUC for the models including the UA PI MoM (AUC 0.731, 95%CI (0.676-0.787), p<0.001) and the CPUR (AUC 0.700, 95%CI (0.638-0.763), p<0.001) compared to the baseline model (p=0.004 and p=0.04, respectively). The highest accuracy in the identification of SGA was associated with the model including UA PI MoM and mean UtA PI MoM (AUC 0.744, 95%CI (0.691-0.796), p<0.001), which yielded a sensitivity of 0.82, 95%CI (0.70-0.91), a specificity of 0.63, 95%CI (0.59-0.67), a PPV of 0.15, 95%CI (0.11-0.19), a NPV of 0.98, 95%CI (0.96-0.99), a LR+ of 2.23, 95%CI (1.91-2.60) and a LR- of 3.59, 95%CI (2.04-6.32). However, the model including UA PI MoM and mean UtA PI MoM was not associated with an improvement in the accuracy of SGA neonates compared to the model including UA PI MoM only (p=0.38).

Table 1 – Demographic features, intrapartum parameters and labor outcomes of the included cases.

	All cases ***N 804***
Age, years ***Mean ± SD***	30.9 ± 5.6
Ethnicity ***N (%)***	White (Caucasian, Arabic) N 658 (81.8%) African N 30 (3.7%) Asian N 56 (7.0%) Other (Caribbean, South American, Mixed) N 60 (7.5%)
Parity ***N (%)***	Nulliparae 441 (54.9%)
Booking BMI, kg/m² ***Mean ± SD***	24.0 ± 4.1
Term pregnancy BMI, kg/m² ***Mean ± SD***	28.5 ± 4.4
Smoking ***N (%)***	Yes 71 (8.8%)
Gestation at delivery, weeks+days ***Mean ± SD***	$39^{+5} \pm 1^{+1}$
PROM at recruitment ***N (%)***	219 (27.2%)
Umbilical artery PI MoM ***Mean ± SD***	1.06 ± 0.21
Middle cerebral artery PI MoM ***Mean ± SD***	0.97 ± 0.21
CPR MoM ***Mean ± SD***	0.94 ± 0.29
Mean UtA PI MoM ***Mean ± SD***	1.16 ± 0.29
Cerebral-placental-uterine ratio ***Mean ± SD***	0.91 ± 0.39
Mode of delivery ***N (%)***	SVD 659 (82.0%) ID 57 (7.1%) CS 88 (10.9%)
Mode of delivery according to indication ***N (%)***	SVD 659 (82.0%) ID fetal distress 29 (3.6%) ID dystocia 28 (3.5%) CS fetal distress 25 (3.1%)

	CS dystocia 63 (7.8%)
Labor length, minutes Mean ± SD	408 ± 205
Fetal Gender N (%)	Male 415 (51.6%)
Birthweight, grams Mean ± SD	3374 ± 424
Birthweight percentile Mean ± SD	50.0 ± 28.6
Apgar at 1 minute Median (range)	9 (1-10)
Apgar at 5 minutes Median (range)	9 (7-10)
Cord arterial pH Median (range) N 699	7.26 ± 0.09
Cord arterial base excess Median (range) N 673	5.79 ± 2.95
Amniotic fluid characteristics N (%)	MSAF 75 (9.3%)
Oxytocin augmentation N (%)	Yes 411 (51.1%)
Epidural in labour N (%)	Yes 475 (59.1%)
Labour length, minutes Mean ± SD	376 ± 195
NICU admission or need for resuscitation at birth N (%)	Yes 12 (1.5%)

SVD: spontaneous vaginal delivery; ID: instrumental delivery; CS: caesarean section; BMI: body mass index; PI: pulsatility index; MSAF: meconium-stained amniotic fluid; NICU: neonatal intensive care unit.

Table 2 – Maternal demographics and intrapartum and perinatal outcomes according to umbilical artery (UA) pulsatility index (PI) MoM.

	Normal UA PI MoM§ N 763	***Increased UA PI MoM§ N 41***	***p***
Age, years Mean ± SD	30.9 ± 5.6	29.7 ± 6.0	0.17
Ethnicity N (%)	White 621 (81.4%) African 29 (3.8%) Asian 54 (7.1%) Other 59 (7.7%)	White 37 (90.2%) African 1 (2.4%) Asian 2 (4.9%) Other 1 (2.4%)	0.51
Parity N (%)	Nulliparae 419 (54.9%)	Nulliparae 22 (53.7%)	0.88
Booking BMI, kg/m^2 Mean ± SD	23.9 ± 4.1	27.7 ± 4.0	<0.001
Term pregnancy BMI, kg/m^2 Mean ± SD	28.3 ± 4.2	31.2 ± 6.8	<0.001
Gestation at delivery, weeks^{+days} Mean ± SD	39^{+6} ± 1^{+1}	40^{+1} ± 0^{+6}	0.03
Mode of delivery N (%)	SVD 629 (82.4%) OI 134 (17.6%)	SVD 30 (73.2%) OI 11 (26.8%)	0.13
Mode of delivery according to indication N (%)	SVD 629 (82.4%) OI dystocia 82 (10.7%) OI distress 52 (6.8%)	SVD 30 (73.2%) OI dystocia 9 (22.0%) OI distress 2 (4.9%)	0.09
Mode of delivery (excluding obstetric intervention due to fetal distress)	SVD 629 (88.5%) OI dystocia 82 (11.5%)	SVD 30 (76.9%) OI dystocia 9 (23.1%)	0.03
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 629 (92.4%) OI distress 52 (7.6%)	SVD 30 (93.8%) OI distress 2 (6.2%)	0.77
Labour length, minutes Mean ± SD	378 ± 194	269 ± 196	0.08

Birthweight, grams Mean ± SD	3374 ± 422	3385 ± 465	0.86
Birthweight percentile Mean ± SD	50.2 ± 28.6	46.6 ± 29.0	0.44
Apgar at 1 minute Median (range)	9 (1-10)	9 (7-10)	<0.001
Apgar at 5 minutes Median (range)	9 (7-10)	9 (9-10)	0.73
Cord arterial pH Mean ± SD N 699	7.25 ± 0.09	7.27 ± 0.06	0.31
Cord arterial base excess Mean ± SD N 673	5.83 ± 2.99	5.12 ± 2.08	0.13
Oxytocin augmentation N (%)	383 (50.2%)	28 (68.3%)	0.02
Epidural in labour N (%)	444 (58.2%)	31 (75.6%)	0.03
Birthweight <10th centile for gestation N (%)	55 (7.2%)	4 (9.8%)	0.54
APGAR <7 at 1 minute N (%)	19 (2.5%)	0 (0.0%)	0.31
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	168 (25.5%)	4 (9.8%)	0.02
Cord arterial pH <7.10 N (%) N 699	20 (3.0%)	1 (2.4%)	0.83
Cord arterial pH <7.00 N (%) N 699	3 (0.5%)	0 (0.0%)	0.67

Cord arterial base excess >8 N (%) N 673	122 (19.3)	3 (7.3%)	0.06
Cord arterial base excess >8 and ≤12 N (%) N 673	99 (15.7%)	3 (7.3%)	0.15
Cord arterial base excess >12 N (%) N 673	23 (3.6%)	0 (0.0%)	0.21
NICU admission or need for resuscitation at birth N (%)	12 (1.6%)	0 (0.0%)	0.42
Hypoxic-ischemic encephalopathy N (%)	-	-	-
Any adverse perinatal outcome* N (%)	224 (29.4%)	5 (12.2%)	0.02
Composite adverse perinatal outcome# N (%)	31 (4.1%)	1 (2.4%)	0.60
Composite neonatal outcome score Mean ± SD	0.47 ± 0.90	0.20 ± 0.60	0.05

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1.

*Any adverse perinatal outcome defined by score ≥1

#Composite adverse perinatal outcome defined by score ≥3

§Raised UA PI MoM defined by UA PI MoM above the 95th percentile of the study population.

Table 3 – Maternal demographics and intrapartum and perinatal outcomes according to middle cerebral artery (MCA) pulsatility index (PI) MoM.

	Reduced MCA PI MoM§ N 37	***Normal MCA PI MoM§ N 767***	***p***
Age, years Mean ± SD	30.5 ± 5.3	30.9 ± 5.6	0.67
Ethnicity N (%)	White 28 (75.7%) African 1 (2.7%) Asian 1 (2.7%) Other 7 (18.9%)	White 630 (82.1%) African 29 (3.8%) Asian 55 (7.2%) Other 53 (6.9%)	0.04
Parity N (%)	Nulliparae 21 (56.8%)	Nulliparae 420 (54.8%)	0.81
Booking BMI, kg/m^2 Mean ± SD	23.8 ± 4.3	24.0 ± 4.1	0.78
Term pregnancy BMI, kg/m^2 Mean ± SD	28.1 ± 4.2	28.5 ± 4.5	0.63
Gestation at delivery, weeks^{+days} Mean ± SD	$38^{+6} \pm 1^{+0}$	$39^{+6} \pm 1^{+1}$	<0.001
Mode of delivery N (%)	SVD 27 (73.0%) OI 10 (27.0%)	SVD 632 (82.4%) OI 135 (17.6%)	0.15
Mode of delivery according to indication N (%)	SVD 27 (73.0%) OI dystocia 4 (10.8%) OI distress 6 (16.2%)	SVD 632 (82.4%) OI dystocia 87 (11.3%) OI distress 48 (6.3%)	0.06
Mode of delivery (excluding obstetric intervention due to fetal distress)	SVD 27 (87.1%) OI dystocia 4 (12.9%)	SVD 632 (87.9%) OI dystocia 87 (12.1%)	0.89
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 27 (81.8%) OI distress 6 (18.2%)	SVD 632 (92.9%) OI distress 48 (7.1%)	0.02
Labour length, minutes Mean ± SD	393 ± 139	375 ± 197	0.65
Birthweight, grams Mean ± SD	3213 ± 372	3382 ± 425	0.02
Birthweight percentile Mean ± SD	48.1 ± 24.0	50.0 ± 28.8	0.44

Apgar at 1 minute Median (range)	9 (4-10)	9 (1-10)	0.91
Apgar at 5 minutes Median (range)	9 (7-10)	9 (7-10)	0.27
Cord arterial pH Mean ± SD N 699	7.24 ± 0.10	7.26 ± 0.09	0.41
Cord arterial base excess Mean ± SD N 673	6.62 ± 4.10	5.75 ± 2.87	0.10
Oxytocin augmentation N (%)	23 (62.2%)	388 (50.6%)	0.17
Epidural in labour N (%)	26 (70.3%)	449 (58.5%)	0.16
Birthweight <10th centile for gestation N (%)	1 (2.7%)	58 (7.6%)	0.27
APGAR <7 at 1 minute N (%)	2 (5.4%)	17 (2.2%)	0.21
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	6 (18.2%)	166 (24.9%)	0.38
Cord arterial pH <7.10 N (%) N 699	2 (6.1%)	19 (2.9%)	0.29
Cord arterial pH <7.00 N (%) N 699	2 (6.1%)	1 (0.2%)	<0.001
Cord arterial base excess >8 N (%) N 673	8 (25.0%)	117 (18.3%)	0.34
Cord arterial base excess >8 and ≤12	4 (12.5%)	98 (15.3%)	0.67

N (%) N 673			
Cord arterial base excess >12 N (%) N 673	4 (12.5%)	19 (3.0%)	0.004
NICU admission or need for resuscitation at birth N (%)	1 (2.7%)	11 (1.4%)	0.53
Hypoxic-ischemic encephalopathy N (%)	-	-	-
Any adverse perinatal outcome* N (%)	9 (24.3%)	220 (28.7%)	0.57
Composite adverse perinatal outcome# N (%)	3 (8.1%)	29 (3.8%)	0.19
Composite neonatal outcome score Mean ± SD	0.68 ± 1.60	0.45 ± 0.84	0.13

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score ≥1

#Composite adverse perinatal outcome defined by score ≥3

§Reduced MCA PI MoM defined by MCA PI MoM below the 5th percentile of the study population

Table 4 – Maternal demographics and intrapartum and perinatal outcomes according to cerebro-placental ratio (CPR) MoM.

	Reduced CPR MoM§ N 75	***Normal CPR MoM§ N 729***	***p***
Age, years Mean ± SD	30.6 ± 5.3	30.9 ± 5.6	0.64
Ethnicity N (%)	White 59 (78.7%) African 3 (4.0%) Asian 7 (9.3%) Other 6 (8.0%)	White 599 (82.2%) African 27 (3.7%) Asian 49 (6.7%) Other 54 (7.4%)	0.85
Parity N (%)	Nulliparae 41 (54.7%)	Nulliparae 400 (54.9%)	0.97
Early pregnancy BMI, kg/m^2 Mean ± SD	25.2 ± 4.5	23.9 ± 4.1	0.009
Term pregnancy BMI, kg/m^2 Mean ± SD	29.1 ± 5.9	28.4 ± 4.3	0.20
Gestation at delivery, weeks^{+d} Mean ± SD	$39^{+2} \pm 1^{+0}$	$39^{+6} \pm 1^{+1}$	<0.001
Mode of delivery N (%)	SVD 48 (64.0%) OI 27 (36.0%)	SVD 611 (83.8%) OI 118 (16.2%)	<0.001
Mode of delivery according to indication N (%)	SVD 48 (64.0%) OI dystocia 4 (5.3%) OI distress 23 (30.7%)	SVD 611 (83.8%) OI dystocia 87 (11.9%) OI distress 31 (4.3%)	<0.001
Mode of delivery (excluding obstetric intervention due to fetal distress)	SVD 48 (92.3%) OI dystocia 4 (7.7%)	SVD 611 (87.5%) OI dystocia 87 (12.5%)	0.31
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 48 (67.6%) OI distress 23 (32.4%)	SVD 611 (95.2%) OI distress 31 (4.8%)	<0.001
Labour length, minutes Mean ± SD	375 ± 187	376 ± 195	0.98
Birthweight, grams Mean ± SD	3290 ± 410	3383 ± 425	0.07
Birthweight percentile Mean ± SD	47.6 ± 27.7	50.2 ± 28.7	0.46

Apgar at 1 minute Median (range)	9 (4-10)	9 (1-10)	0.66
Apgar at 5 minutes Median (range)	9 (7-10)	9 (7-10)	0.04
Cord arterial pH Mean ± SD N 699	7.22 ± 0.10	7.26 ± 0.09	<0.001
Cord arterial base excess Mean ± SD N 673	6.64 ± 3.30	5.70 ± 2.89	0.01
Oxytocin augmentation N (%)	49 (65.3%)	362 (49.7%)	0.01
Epidural in labour N (%)	55 (73.3%)	420 (57.6%)	0.008
Birthweight <10th centile for gestation N (%)	7 (9.3%)	52 (7.1%)	0.49
APGAR <7 at 1 minute N (%)	6 (8.0%)	13 (1.8%)	0.001
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	26 (37.7%)	146 (23.2%)	0.008
Cord arterial pH <7.10 N (%) N 699	8 (11.6%)	13 (2.1%)	<0.001
Cord arterial pH <7.00 N (%) N 699	2 (2.9%)	1 (0.2%)	0.001
Cord arterial base excess >8 N (%) N 673	16 (24.2%)	109 (18.0%)	0.21
Cord arterial base excess >8 and ≤12	11 (16.7%)	91 (15.0%)	0.72

N (%) ***N 673***			
Cord arterial base excess >12 ***N (%)*** ***N 673***	5 (7.6%)	18 (3.0%)	0.05
NICU admission or need for resuscitation at birth ***N (%)***	5 (6.7%)	7 (1.0%)	<0.001
Hypoxic-ischemic encephalopathy ***N (%)***	-	-	-
Any adverse perinatal outcome* ***N (%)***	29 (38.7%)	200 (27.4%)	0.04
Composite adverse perinatal outcome# ***N (%)***	10 (13.3%)	22 (3.0%)	<0.001
Composite neonatal outcome score ***Mean ± SD***	0.91 ± 1.50	0.41 ± 0.78	<0.001

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) 2. Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score ≥1

#Composite adverse perinatal outcome defined by score ≥3

§Reduced CPR defined by CPR MoM within the lowest decile

Table 5 – Maternal demographics and intrapartum and perinatal outcomes according to mean uterine artery (UtA) pulsatility index (PI) MoM.

	Normal UtA PI MoM§ N 764	***Increased UtA PI MoM§ N 40***	***p***
Age, years Mean ± SD	30.9 ± 5.6	30.6 ± 5.3	0.77
Ethnicity N (%)	White 628 (82.2%) African 30 (3.9%) Asian 53 (6.9%) Other 53 (6.9%)	White 30 (75.0%) African 0 (0.0%) Asian 3 (7.5%) Other 7 (17.5%)	0.06
Parity N (%)	Nulliparae 419 (54.8%)	Nulliparae 22 (55.0%)	0.98
Early pregnancy BMI, kg/m^2 Mean ± SD	24.1 ± 4.2	23.4 ± 3.2	0.33
Term pregnancy BMI, kg/m^2 Mean ± SD	28.5 ± 4.5	28.1 ± 3.7	0.63
Gestation at delivery, weeks^{+days} Mean ± SD	$39^{+6} \pm 1^{+1}$	$39^{+5} \pm 1^{+1}$	0.55
Mode of delivery N (%)	SVD 632 (82.7%) OI 132 (17.3%)	SVD 27 (67.5%) OI 13 (32.5%)	0.02
Mode of delivery according to indication N (%)	SVD 632 (82.7%) OI dystocia 85 (11.1%) OI distress 47 (6.2%)	SVD 27 (67.5%) OI dystocia 6 (15.0%) OI distress 7 (17.5%)	0.01
Mode of delivery (excluding obstetric intervention due to fetal distress)	SVD 632 (88.1%) OI dystocia 85 (11.9%)	SVD 27 (81.8%) OI dystocia 6 (18.2%)	0.28
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 632 (93.1%) OI distress 47 (6.9%)	SVD 27 (79.4%) OI distress 7 (20.6%)	0.003
Labour length, minutes Mean ± SD	377 ± 195	354 ± 187	0.50
Birthweight, grams Mean ± SD	3385 ± 421	3171 ± 427	0.002
Birthweight percentile Mean ± SD	50.6 ± 28.5	37.1 ± 28.1	0.004
Apgar at 1 minute	9 (1-10)	9 (6-10)	0.10

Median (range)			
Apgar at 5 minutes Median (range)	9 (7-10)	9 (7-10)	0.50
Cord arterial pH Mean ± SD N 699	7.25 ± 0.09	7.27 ± 0.09	0.36
Cord arterial base excess Mean ± SD N 673	5.75 ± 2.91	6.51 ± 3.46	0.13
Oxytocin augmentation N (%)	396 (51.8%)	15 (37.5%)	0.08
Epidural in labour N (%)	458 (59.9%)	17 (42.5%)	0.03
Birthweight <10th centile for gestation N (%)	51 (6.7%)	8 (20.0%)	0.002
APGAR <7 at 1 minute N (%)	18 (2.4%)	1 (2.5%)	0.95
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	167 (25.2%)	5 (13.5%)	0.11
Cord arterial pH <7.10 N (%) N 699	20 (3.0%)	1 (2.7%)	0.91
Cord arterial pH <7.00 N (%) N 699	3 (0.5%)	0 (0.0%)	0.68
Cord arterial base excess >8 N (%) N 673	115 (18.1%)	10 (27.0%)	0.17
Cord arterial base excess >8 and ≤12 N (%) N 673	96 (15.1%)	6 (16.2%)	0.85
Cord arterial base excess >12	19 (3.0%)	4 (10.8%)	0.01

N (%) ***N 673***			
NICU admission or need for resuscitation at birth ***N (%)***	9 (1.2%)	3 (7.5%)	0.001
Hypoxic-ischemic encephalopathy ***N (%)***	-	-	-
Any adverse perinatal outcome* ***N (%)***	217 (28.4%)	12 (30.0%)	0.83
Composite adverse perinatal outcome[#] ***N (%)***	29 (3.8%)	3 (7.5%)	0.24
Composite neonatal outcome score ***Mean ± SD***	0.45 ± 0.87	0.60 ± 1.11	0.30

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score ≥1

[#]Composite adverse perinatal outcome defined by score ≥3

[§]Raised UtA PI MoM defined by UtA PI MoM above the 95th percentile of the study population

Table 6 – Maternal demographics and intrapartum and perinatal outcomes according to the cerebral-placental-uterine ratio (CPUR).

	Reduced CPUR§ N 75	***Normal CPUR § N 729***	***p***
Age, years Mean ± SD	29.9 ± 5.6	31.0 ± 5.6	0.13
Ethnicity N (%)	White 628 (82.2%) African 30 (3.9%) Asian 53 (6.9%) Other 53 (6.9%)	White 30 (75.0%) African 0 (0.0%) Asian 3 (7.5%) Other 7 (17.5%)	0.06
Parity N (%)	Nulliparae 419 (54.8%)	Nulliparae 22 (55.0%)	0.98
Booking BMI, kg/m^2 Mean ± SD	25.0 ± 4.2	23.9 ± 4.1	0.04
Term pregnancy BMI, kg/m^2 Mean ± SD	29.3 ± 4.9	28.4 ± 4.4	0.10
Gestation at delivery, weeks^{+days} Mean ± SD	$39^{+3} \pm 1^{+0}$	$39^{+6} \pm 1^{+1}$	0.005
Mode of delivery N (%)	SVD 46 (61.3%) OI 29 (38.7%)	SVD 613 (84.1%) OI 116 (15.9%)	<0.001
Mode of delivery according to indication N (%)	SVD 46 (61.3%) OI dystocia 8 (10.7%) OI distress 21 (28.0%)	SVD 613 (84.1%) OI dystocia 83 (11.4%) OI distress 33 (4.5%)	<0.001
Mode of delivery (excluding obstetric intervention due to fetal distress) N (%)	SVD 46 (85.2%) OI dystocia 8 (14.8%)	SVD 613 (88.1%) OI dystocia 83 (11.9%)	0.53
Mode of delivery (excluding obstetric intervention for dystocia) N (%)	SVD 46 (68.7%) OI distress 21 (31.3%)	SVD 613 (94.9%) OI distress 33 (5.1%)	<0.001
Labour length, minutes Mean ± SD	382 ± 195	376 ± 195	0.84
Birthweight, grams Mean ± SD	3251 ± 431	3387 ± 422	0.008
Birthweight percentile Mean ± SD	44.3 ± 28.6	50.6 ± 28.6	0.07
Apgar at 1 minute Median (range)	9 (1-10)	9 (4-10)	0.88
Apgar at 5 minutes	9 (7-10)	9 (7-10)	0.27

Median (range)			
Cord arterial pH Mean ± SD N 699	7.23 ± 0.11	7.26 ± 0.09	0.02
Cord arterial base excess Mean ± SD N 673	6.72 ± 3.62	5.68 ± 2.84	0.005
Oxytocin augmentation N (%)	41 (54.7%)	370 (50.8%)	0.52
Epidural in labour N (%)	47 (62.7%)	428 (58.7%)	0.51
Birthweight <10th centile for gestation N (%)	9 (12.0%)	50 (6.9%)	0.10
APGAR <7 at 1 minute N (%)	6 (8.0%)	13 (1.8%)	0.001
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	21 (30.0%)	151 (24.0%)	0.27
Cord arterial pH <7.10 N (%) N 699	7 (10.0%)	14 (2.2%)	<0.001
Cord arterial pH <7.00 N (%) N 699	2 (2.9%)	1 (0.2%)	0.001
Cord arterial base excess >8 N (%) N 673	19 (27.5%)	106 (17.5%)	0.04
Cord arterial base excess >8 and ≤12 N (%) N 673	10 (14.5%)	92 (15.2%)	0.87
Cord arterial base excess >12 N (%) N 673	9 (13.0%)	14 (2.3%)	<0.001

NICU admission or need for resuscitation at birth N (%)	4 (5.3%)	8 (1.1%)	0.004
Hypoxic-ischemic encephalopathy N (%)	-	-	-
Any adverse perinatal outcome* N (%)	27 (36.0%)	202 (27.7%)	0.13
Composite adverse perinatal outcome[#] N (%)	10 (13.3%)	22 (3.0%)	<0.001
Composite neonatal outcome score Mean ± SD	0.91 ± 1.54	0.41 ± 0.78	<0.001

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score ≥1

[#]Composite adverse perinatal outcome defined by score ≥3

[§]Reduced CPUR defined by CPUR within the lowest decile of the study population

Table 7 – Maternal demographics and intrapartum and perinatal outcomes according to mode of delivery: spontaneous vaginal delivery (SVD), all obstetric interventions and obstetric intervention due to fetal distress.

p1 SVD vs obstetric intervention; p2 SVD vs obstetric intervention due to dystocia; p3 SVD vs obstetric intervention due to fetal distress; p4 SVD vs obstetric intervention due to dystocia vs obstetric intervention due to fetal distress (chi-square, ANOVA, Kruskal-Wallis)

Composite neonatal outcome scored as follows: 1) Apgar $\geq$7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH $\geq$7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess $\leq$8 = 0, > 8 and $\leq$12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score $\geq$1

#Composite adverse perinatal outcome defined by score $\geq$3

	Spontaneous vaginal delivery N 659 (82.0%)	*Obstetric intervention N 145 (18.0%)*	*Obstetric intervention due to dystocia N 91 (11.3%)*	*Obstetric intervention due to fetal distress N 54 (6.7%)*	*p1*	*p2*	*p3*	*p4*
Age, years Mean ± SD	30.9 ± 5.6	30.5 ± 5.6	30.5 ± 5.2	30.7 ± 6.1	0.41	0.42	0.70	0.69
Ethnicity N (%)	White 545 (82.7%) African 24 (3.6%) Asian 45 (6.8%) Other 45 (6.8%)	White 113 (77.9%) African 6 (4.1%) Asian 11 (7.6%) Other 15 (10.3%)	White 73 (80.2%) African 3 (3.3%) Asian 5 (5.5%) Other 10 (11.0%)	White 40 (74.1%) African 3 (5.6%) Asian 6 (11.1%) Other 5 (9.3%)	0.48	0.54	0.45	0.57
Parity N (%)	Nulliparae 339 (51.4%)	Nulliparae 102 (70.3%)	Nulliparae 63 (69.2%)	Nulliparae 39 (72.2%)	<0.001	0.001	0.003	<0.001
Booking BMI, kg/m² Mean ± SD	24.0 ± 4.3	25.1 ± 4.5	25.6 ± 4.4	24.2 ± 4.6	0.005	0.001	0.74	0.003
Term pregnancy BMI, kg/m² Mean ± SD	28.2 ± 4.4	29.5 ± 4.7	30.2 ± 4.4	28.5 ± 4.9	0.002	<0.001	0.71	0.001
Smoking N (%)	57 (8.6%)	14 (9.7%)	10 (11.0%)	4 (7.4%)	0.70	0.46	0.75	0.71
Gestation at delivery, weeks+days Mean ± SD	$39^{+6} \pm 1^{+1}$	$39^{+6} \pm 1^{+0}$	$40^{+0} \pm 1^{+0}$	$39^{+5} \pm 1^{+0}$	0.19	0.03	0.54	0.06
PROM at recruitment N (%)	178 (27.0%)	41 (28.3%)	28 (30.8%)	13 (24.1%)	0.76	0.45	0.64	0.65
Umbilical PI MoM Mean ± SD	1.04 ± 0.21	1.12 ± 0.23	1.12 ± 0.23	1.12 ± 0.23	<0.001	0.002	0.007	0.001
Middle cerebral artery PI MoM Mean ± SD	0.98 ± 0.22	0.95 ± 0.21	0.99 ± 0.20	0.89 ± 0.20	0.17	0.72	0.004	0.01
CPR MoM Mean ± SD	0.96 ± 0.29	0.84 ± 0.27	0.90 ± 0.25	0.76 ± 0.27	<0.001	0.04	<0.001	<0.001
UCR MoM Mean ± SD	1.26 ± 0.36	1.39 ± 0.41	1.33 ± 0.33	1.51 ± 0.50	<0.001	0.10	<0.001	<0.001
Mean UtA PI MoM Mean ± SD	1.10 ± 0.27	1.20 ± 0.35	1.18 ± 0.32	1.23 ± 0.39	<0.001	0.006	0.001	<0.001

CPUR ***Mean ± SD***	0.94 ± 0.40	0.76 ± 0.33	0.81 ± 0.30	0.69 ± 0.36	<0.001	0.003	<0.001	<0.001
Labour length, minutes ***Mean + SD***	355 ± 182	526 ± 219	598 ± 194	456 ± 221	<0.001	<0.001	0.001	<0.001
Fetal Gender ***N (%)***	Male 345 (52.4%)	Male 70 (48.3%)	Male 41 (45.1%)	Male 29 (53.7%)	0.37	0.19	0.85	0.41
Birthweight, grams ***Mean + SD***	3369 ± 419	3409 ± 446	3442 ± 437	3352 ± 461	0.29	0.11	0.81	0.27
Birthweight percentile ***Mean ± SD***	50.0 ± 28.3	50.9 ± 29.9	52.4 ± 29.7	48.3 ± 30.4	0.67	0.41	0.72	0.64
Apgar at 1 minute ***Median (range)***	9 (3-10)	9 (1-10)	9 (2-10)	9 (1-10)	0.02	0.37	<0.001	<0.001
Apgar at 5 minutes ***Median (range)***	9 (8-10)	9 (7-10)	9 (7-10)	9 (7-10)	0.48	0.07	<0.001	<0.001
Cord arterial pH ***Mean ± SD*** ***N 699***	7.26 ± 0.09	7.24 ± 0.09	7.27 ± 0.07	7.19 ± 0.10	0.006	0.49	<0.001	<0.001
Cord arterial base excess ***Mean ± SD*** ***N 673***	5.68 ± 2.83	6.28 ± 3.36	5.59 ± 2.68	7.43 ± 4.04	0.04	0.81	<0.001	<0.001
Amniotic fluid characteristics in labour ***N (%)***	MSAF 55 (8.3%)	MSAF 20 (13.8%)	MSAF 11 (12.1%)	MSAF 9 (16.7%)	0.04	0.24	0.04	0.08
Oxytocin augmentation ***N (%)***	Yes 309 (46.9%)	Yes 102 (70.3%)	Yes N 70 (76.9%)	Yes 32 (59.3%)	<0.001	<0.001	0.08	<0.001
Epidural in labour ***N (%)***	Yes 362 (54.9%)	Yes 113 (77.9%)	Yes 77 (84.6%)	Yes 36 (66.7%)	<0.001	<0.001	0.10	<0.001
Birthweight <10th centile for gestation ***N (%)***	45 (6.8%)	14 (9.7%)	9 (9.9%)	5 (9.3%)	0.24	0.29	0.50	0.49
APGAR <7 at 1 minute ***N (%)***	4 (0.6%)	15 (10.3%)	5 (5.5%)	10 (18.5%)	<0.001	<0.001	<0.001	<0.001
APGAR <7 at 5 minutes ***N (%)***	-	-	-	-	-	-	-	-
Cord arterial pH <7.20 ***N (%)*** ***N 699***	130 (23.0%)	42 (31.6%)	16 (19.3%)	26 (52.0%)	0.04	0.45	<0.001	<0.001

Cord arterial pH <7.10 N (%) N 699	11 (1.9%)	10 (7.5%)	0 (0%)	10 (20.0%)	0.001	0.20	<0.001	<0.001
Cord arterial pH <7.00 N (%) N 699	1 (0.2%)	2 (1.5%)	0 (0%)	2 (4.0%)	0.04	0.70	<0.001	<0.001
Cord arterial base excess >8 N (%) N 673	92 (16.9%)	33 (25.8%)	13 (16.2%)	20 (41.7%)	0.02	0.89	<0.001	<0.001
Cord arterial base excess >8 and ≤12 N (%) N 673	77 (14.5%)	25 (19.5%)	10 (12.5%)	15 (31.2%)	0.12	0.69	0.002	0.005
Cord arterial base excess >12 N (%) N 673	15 (2.8%)	8 (6.2%)	3 (3.8%)	5 (10.4%)	0.05	0.62	0.005	0.02
NICU admission or need for resuscitation at birth N (%)	6 (0.9%)	6 (4.1%)	1 (1.1%)	5 (9.3%)	0.004	0.86	<0.001	<0.001
Hypoxic-ischemic encephalopathy N (%)	-	-	-	-	-	-	-	-
Any adverse perinatal outcome* N (%)	173 (26.3%)	56 (38.6%)	25 (27.5%)	31 (57.4%)	0.003	0.80	<0.001	<0.001
Composite adverse perinatal outcome* N (%)	17 (2.6%)	15 (10.3%)	2 (2.2%)	13 (24.1%)	<0.001	0.83	<0.001	<0.001
Composite neonatal outcome score Mean ± SD	0.38 ± 0.76	0.79 ± 1.28	0.41 ± 0.75	1.44 ± 1.67	<0.001	0.79	<0.001	<0.001

Figure 1 – Receiver–operating characteristics (ROC) curve analysis for obstetric intervention due to intrapartum fetal distress according to the model combining the CPR MoM <10th percentile and the mean UtA PI MoM >95th percentile (blue line), the model including the CPR MoM <10th percentile alone (green line), the model including the CPR MoM <10th percentile OR the mean UtA PI MoM >95th percentile (red line) and the model including the CPR MoM <10th percentile AND the mean UtA PI MoM >95th percentile (black line).

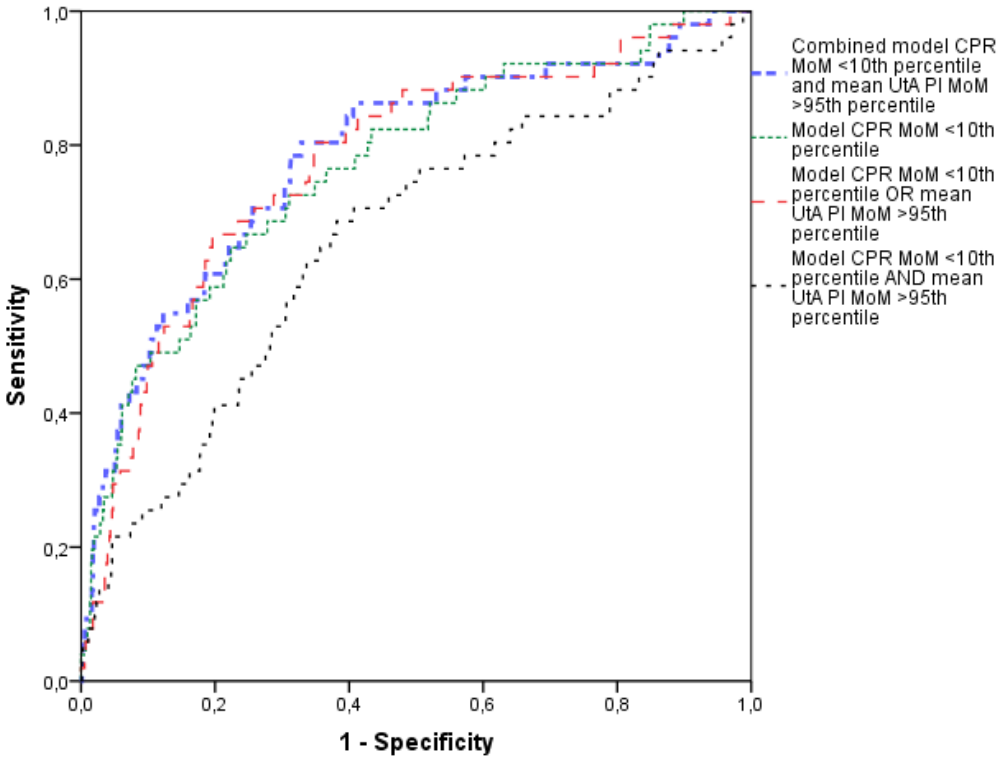


Table 8 – Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios (LR+ and LR-) for the identification of cases of obstetric intervention due to suspected intrapartum fetal compromise in cases with cerebroplacental ratio (CPR) MoM <10th percentile, in cases with CPR MoM <10th percentile and/or mean uterine artery (UtA) pulsatility index (PI) MoM >95th percentile and for the gestational age, for the models obtained by combining the baseline characteristics with the CPR MoM <10th percentile, the CPR MoM <10th percentile and/or the mean UtA PI MoM >95th percentile and for the combined model including the CPR MoM <10th percentile and the mean UtA PI MoM >95th percentile.

	CPR MoM <10th percentile	**CPR MoM <10th percentile and/or UtA PI MoM >95th percentile**	**CPR MoM <10th percentile and UtA PI MoM >95th percentile**	**Model CPR MoM <10th percentile**	**Model CPR MoM <10th percentile and/or UtA PI MoM >95th percentile**	**Model CPR MoM <10th percentile and UtA PI MoM >95th percentile**	**Model CPR MoM <10th percentile + UtA PI MoM >95th percentile**
Sensitivity	0.42, 95% CI (0.29 – 0.57)	0.48, 95% CI (0.34 – 0.62)	0.07, 95% CI (0.02 – 0.18)	0.65, 95% CI (0.50 – 0.78)	0.67, 95% CI (0.52 – 0.79)	0.69, 95% CI (0.54 – 0.81)	0.78, 95% CI (0.65 – 0.89)
Specificity	0.93, 95% CI (0.91 – 0.95)	0.89, 95% CI (0.86 – 0.91)	0.99, 95% CI (0.99 – 1.00)	0.77, 95% CI (0.74 – 0.80)	0.80, 95% CI (0.77 – 0.83)	0.62, 95% CI (0.58 – 0.65)	0.68, 95% CI (0.65 – 0.72)
PPV	0.31, 95% CI (0.21 – 0.42)	0.24, 95% CI (0.16 – 0.33)	0.67, 95% CI (0.22 – 0.96)	0.17, 95% CI (0.12 – 0.22)	0.19, 95% CI (0.14 – 0.26)	0.11, 95% CI (0.08 – 0.15)	0.15, 95% CI (0.11 – 0.19)
NPV	0.96, 95% CI (0.94 – 0.97)	0.96, 95% CI (0.94 – 0.97)	0.94, 95% CI (0.92 – 0.95)	0.97, 95% CI (0.95 – 0.98)	0.97, 95% CI (0.96 – 0.98)	0.97, 95% CI (0.95 – 0.98)	0.98, 95% CI (0.96 – 0.99)
LR +	6.14, 95% CI (4.09 – 9.22)	4.35, 95% CI (3.09 – 6.13)	27.78, 95% CI (5.20 – 148.26)	2.86, 95% CI (2.24 – 3.65)	3.40, 95% CI (2.66 – 4.33)	1.80, 95% CI (1.46 – 2.21)	2.48, 95% CI (2.07 – 2.97)
LR -	1.62, 95% CI (1.29 – 2.04)	1.72, 95% CI (1.32 – 2.22)	1.08, 95% CI (1.00 – 1.16)	2.19, 95% CI (1.51 – 3.19)	2.41, 95% CI (1.63 – 3.56)	1.97, 95% CI (1.31 – 2.97)	3.17, 95% CI (1.87 – 5.36)

Table 9 – Maternal demographics, maternal and fetal Doppler and intrapartum and perinatal outcomes according to the occurrence of abnormal cord gases[#] (73 cases with missing data).

[#]Abnormal arterial cord gases defined as either cord arterial pH <7.10 or cord arterial base excess >12

	Abnormal arterial cord gases N 38 (5.2%)	***Normal arterial cord gases N 693 (94.8%)***	***p***
Age, years Mean ± SD	30.9 ± 5.98	30.7 ± 5.6	0.86
Ethnicity N (%)	White 35 (92.1%) African 0 (0.0%) Asian 1 (2.6%) Other 2 (5.3%)	White 568 (82.0%) African 24 (3.5%) Asian 45 (6.5%) Other 56 (8.1%)	0.40
Parity N (%)	Nulliparae 32 (84.2%)	Nulliparae 376 (54.3%)	<0.001
Booking BMI, kg/m^2 Mean ± SD	23.8 ± 4.0	24.3 ± 4.4	0.51
Term pregnancy BMI, kg/m^2 Mean ± SD	28.3 ± 3.8	28.6 ± 4.5	0.71
Smoking N (%)	0 (0.0%)	68 (9.8%)	0.04
Gestation at delivery, weeks^{+days} Mean ± SD	$39^{+6} \pm 1^{+0}$	$39^{+6} \pm 1^{+1}$	0.74
PROM at recruitment N (%)	14 (36.8%)	182 (26.3%)	0.15
Mode of delivery N (%)	SVD 23 (60.5%) OI 15 (39.5%)	SVD 571 (82.4%) OI 122 (17.6%)	0.001
Mode of delivery according to indication N (%)	SVD 23 (60.5%) OI dystocia 3 (7.9%) OI distress 12 (31.6%)	SVD 571 (82.4%) OI dystocia 83 (12.0%) OI distress 39 (5.6%)	<0.001
Mode of delivery (excluding obstetric intervention	SVD 23 (88.5%) OI dystocia 3 (11.5%)	SVD 571 (87.3%) OI dystocia 83 (12.7%)	0.86

due to fetal distress)			
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 23 (65.7%) OI distress 12 (34.3%)	SVD 571 (93.6%) OI distress 39 (6.4%)	<0.001
Umbilical PI MoM Mean ± SD	1.02 ± 0.23	1.07 ± 0.21	0.21
Middle cerebral artery PI MoM Mean ± SD	0.90 ± 0.19	0.97 ± 0.21	0.045
CPR MoM Mean ± SD	0.89 ± 0.29	0.93 ± 0.28	0.34
UCR MoM Mean ± SD	1.36 ± 0.49	1.30 ± 0.36	0.27
Mean UtA PI MoM Mean ± SD	1.26 ± 0.30	1.12 ± 0.29	0.004
CPUR Mean ± SD	0.77 ± 0.39	0.89 ± 0.38	0.05
Labour length, minutes Mean ± SD	490 ± 196	373 ± 194	0.001
Fetal Gender N (%)	Male 21 (55.3%)	Male 354 (51.1%)	0.62
Amniotic fluid characteristics in labour N (%)	MSAF 5 (13.2%)	MSAF 65 (9.4%)	0.44
Oxytocin augmentation N (%)	Yes 28 (73.7%)	Yes 362 (52.2%)	0.01
Epidural in labour N (%)	Yes 29 (76.3%)	Yes 412 (59.5%)	0.04

Figure 2 – Receiver–operating characteristics (ROC) curve analysis for abnormal cord gases at birth according to the baseline and a model including baseline characteristics (blue line) and mean UtA PI MoM (green line).

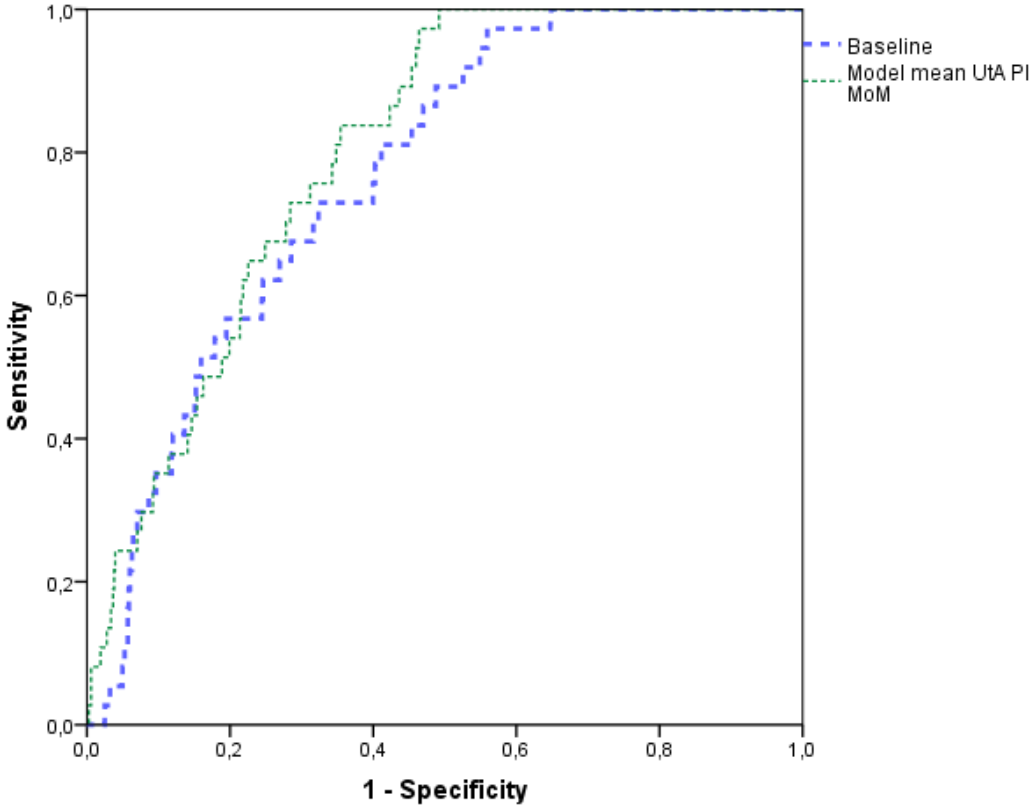


Table 10 – Maternal demographics and intrapartum and perinatal outcomes according to composite adverse perinatal outcome[#].

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

[#]Composite adverse perinatal outcome defined by score ≥3

	Composite adverse perinatal outcome N 32 (4.0%)	***Normal perinatal outcome N 772 (96.0%)***	***p***
Age, years Mean ± SD	31.2 ± 6.2	30.9 ± 5.6	0.77
Ethnicity N (%)	White 28 (86.6%) African 0 (0.0%) Asian 2 (6.2%) Other 2 (6.2%)	White 630 (81.6%) African 30 (3.9%) Asian 54 (7.0%) Other 58 (7.5%)	0.69
Parity N (%)	Nulliparae 27 (84.4%)	Nulliparae 414 (53.6%)	<0.001
Booking BMI, kg/m² Mean ± SD	24.1 ± 4.2	24.2 ± 4.4	0.89
Term pregnancy BMI, kg/m² Mean ± SD	28.4 ± 3.9	28.5 ± 4.5	0.95
Smoking N (%)	0 (0.0%)	71 (9.2%)	0.07
Gestation at delivery, weeks+days Mean ± SD	$40^{+0} \pm 0^{+5}$	$39^{+5} \pm 1^{+1}$	0.45
PROM at recruitment N (%)	10 (31.2%)	209 (27.1%)	0.60
Mode of delivery N (%)	SVD 17 (53.1%) OI 15 (46.9%)	SVD 642 (83.2%) OI 130 (16.8%)	<0.001
Mode of delivery according to indication N (%)	SVD 17 (53.1%) OI dystocia 2 (6.2%) OI distress 13 (40.6%)	SVD 642 (83.2%) OI dystocia 89 (11.5%) OI distress 41 (5.3%)	<0.001
Mode of delivery (excluding obstetric	SVD 17 (89.5%) OI dystocia 2 (10.5%)	SVD 642 (87.8%) OI dystocia 89 (12.2%)	0.83

intervention due to fetal distress)			
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 17 (56.7%) OI distress 13 (43.3%)	SVD 642 (94.0%) OI distress 41 (6.0%)	<0.001
Umbilical PI MoM Mean ± SD	1.03 ± 0.24	1.06 ± 0.21	0.50
Middle cerebral artery PI MoM Mean ± SD	0.88 ± 0.17	0.98 ± 0.21	0.01
CPR MoM Mean ± SD	0.86 ± 0.29	0.94 ± 0.29	0.11
UCR MoM Mean ± SD	1.40 ± 0.50	1.28 ± 0.36	0.07
Mean UtA PI MoM Mean ± SD	1.24 ± 0.32	1.11 ± 0.29	0.02
CPUR Mean ± SD	0.69 ± 0.24	0.92 ± 0.40	0.04
Labour length, minutes Mean ± SD	488 ± 184	371 ± 194	0.003
Fetal Gender N (%)	Male 19 (59.4%)	Male 396 (51.3%)	0.37
Amniotic fluid characteristics in labour N (%)	MSAF 5 (15.6%)	MSAF 70 (9.1%)	0.21
Oxytocin augmentation N (%)	Yes 23 (71.9%)	Yes 388 (50.3%)	0.02
Epidural in labour N (%)	Yes 24 (75.0%)	Yes 451 (58.4%)	0.06

Figure 3 – Receiver–operating characteristics (ROC) curve analysis for composite adverse perinatal outcome according to the baseline model (blue line), the model including the MCA PI MoM (green line), the model including the mean UtA PI MoM (red line) and a combined model including MCA PI MoM and mean UtA PI MoM (black line).

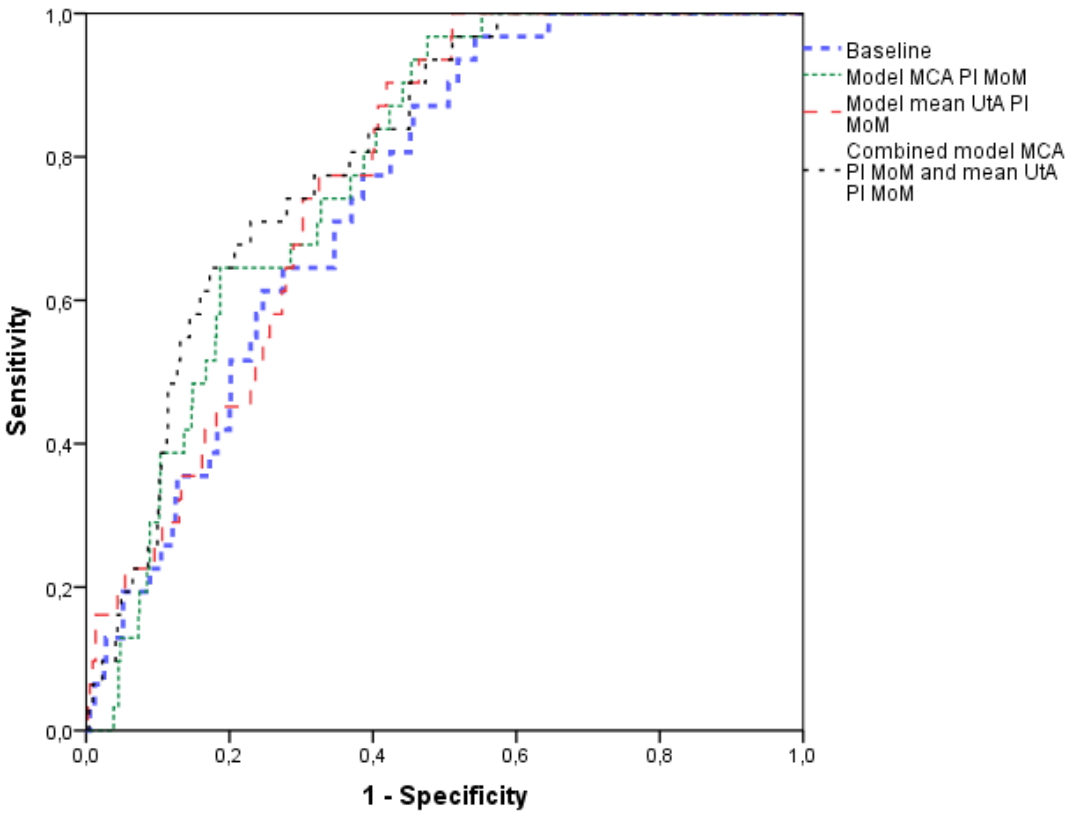


Table 11 – Maternal demographics and intrapartum and perinatal outcomes according to birthweight <10th centile for the gestation.

	Birthweight <10th centile N 59 (7.3%)	***Birthweight ≥10th centile N 745 (92.7%)***	***p***
Age, years Mean ± SD	30.9 ± 5.9	30.9 ± 5.6	0.93
Ethnicity N (%)	White 47 (79.7%) African 2 (3.4%) Asian 7 (11.9%) Other 3 (5.1%)	White 611 (82.0%) African 28 (3.8%) Asian 49 (6.6%) Other 57 (7.7%)	0.44
Parity N (%)	Nulliparae 35 (59.3%)	Nulliparae 406 (54.5%)	0.47
Booking BMI, kg/m² Mean ± SD	25.0 ± 4.0	24.1 ± 4.4	0.13
Term pregnancy BMI, kg/m² Mean ± SD	29.0 ± 4.2	28.4 ± 4.5	0.38
Smoking N (%)	6 (10.2%)	65 (8.7%)	0.71
Gestation at delivery, weeks+days Mean ± SD	$39^{+6} \pm 1^{+0}$	$39^{+6} \pm 1^{+1}$	0.55
PROM at recruitment N (%)	17 (28.8%)	202 (27.1%)	0.78
Mode of delivery N (%)	SVD 45 (76.3%) OI 14 (23.7%)	SVD 614 (82.4%) OI 131 (17.6%)	0.24
Mode of delivery according to indication N (%)	SVD 45 (76.3%) OI dystocia 9 (15.3%) OI distress 5 (8.5%)	SVD 614 (82.4%) OI dystocia 82 (11.0%) OI distress 49 (6.6%)	0.49
Mode of delivery (excluding obstetric intervention due to fetal distress)	SVD 45 (83.3%) OI dystocia 9 (16.7%)	SVD 614 (88.2%) OI dystocia 82 (11.8%)	0.29
Mode of delivery (excluding obstetric intervention for dystocia)	SVD 45 (90.0%) OI distress 5 (10.0%)	SVD 614 (92.6%) OI distress 49 (7.4%)	0.50
Umbilical PI MoM Mean ± SD	1.21 ± 0.18	1.05 ± 0.21	<0.001
Middle cerebral artery PI MoM Mean ± SD	0.97 ± 0.18	0.97 ± 0.22	0.83

CPR MoM Mean ± SD	0.80 ± 0.16	0.95 ± 0.29	<0.001
UCR MoM Mean ± SD	1.46 ± 0.30	1.27 ± 0.37	<0.001
Mean UtA PI MoM Mean ± SD	1.25 ± 0.39	1.11 ± 0.28	<0.001
CPUR Mean ± SD	0.69 ± 0.24	0.92 ± 0.40	<0.001
Labour length, minutes Mean ± SD	337 ± 179	378 ± 196	0.26
Fetal Gender N (%)	Male 70 (48.3%)	Male 345 (52.4%)	0.85
Apgar at 1 minute Median (range)	9 (6-10)	9 (1-10)	0.31
Apgar at 5 minutes Median (range)	10 (7-10)	9 (7-10)	0.12
Cord arterial pH Mean ± SD N 699	7.25 ± 0.08	7.26 ± 0.09	0.85
Cord arterial base excess Mean ± SD N 673	5.72 ± 2.27	5.80 ± 3.00	0.86
Amniotic fluid characteristics in labour N (%)	MSAF 6 (10.2%)	MSAF 69 (9.3%)	0.82
Oxytocin augmentation N (%)	Yes 37 (62.7%)	Yes 374 (50.2%)	0.06
Epidural in labour N (%)	Yes 42 (71.2%)	Yes 433 (58.1%)	0.049
APGAR <7 at 1 minute N (%)	2 (3.4%)	17 (2.3%)	0.59
APGAR <7 at 5 minutes N (%)	-	-	-
Cord arterial pH <7.20 N (%) N 699	14 (28.0%)	158 (24.3%)	0.56
Cord arterial pH <7.10 N (%) N 699	1 (2.0%)	20 (3.1%)	0.67

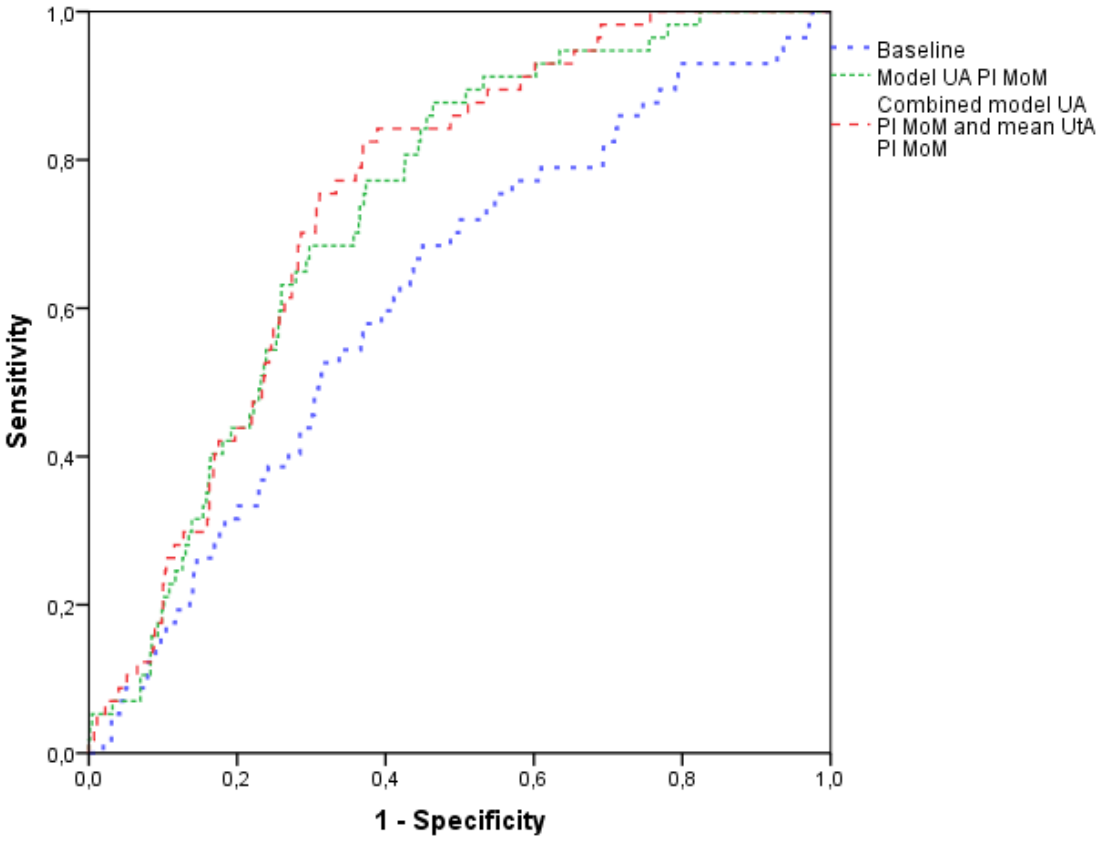
Cord arterial pH <7.00 N (%) N 699	0 (0.0%)	3 (0.5%)	0.63
Cord arterial base excess >8 N (%) N 673	10 (18.5%)	115 (18.6%)	0.99
Cord arterial base excess >8 and ≤12 N (%) N 673	10 (18.5%)	92 (14.9%)	0.47
Cord arterial base excess >12 N (%) N 673	0 (0.0%)	23 (3.7%)	0.15
NICU admission or need for resuscitation at birth N (%)	2 (3.4%)	10 (1.3%)	0.21
Hypoxic-ischemic encephalopathy N (%)	-	-	-
Any adverse perinatal outcome* N (%)	21 (35.6%)	208 (27.9%)	0.21
Composite adverse perinatal outcome# N (%)	1 (1.7%)	31 (4.2%)	0.35
Composite neonatal outcome score Mean ± SD	0.49 ± 0.86	0.46 ± 0.89	0.76

Composite neonatal outcome scored as follows: 1) Apgar ≥7 @ 1 min = 0, <7 @ 1 min = 1, <7 @ 5 min = 2; 2) Cord arterial pH ≥7.20 = 0, <7.20 = 1, <7.10 = 2, <7.00 = 3; 3) Base excess ≤8 = 0, > 8 and ≤12 = 1, >12 = 2; 4) NICU admission or need for resuscitation No = 0, Yes = 1

*Any adverse perinatal outcome defined by score ≥1

#Composite adverse perinatal outcome defined by score ≥3

Figure 4 – Receiver–operating characteristics (ROC) curve analysis for postnatal diagnosis of small-for-gestational age according to the baseline model (blue line), the model including the UA PI MoM (green line) and the model including UA PI MoM and mean UtA PI MoM (red line).



Discussion

In this prospective observational study including a selected cohort of women with low risk singleton term pregnancy in early labour we demonstrate an association between maternal and fetal Doppler parameters measured in early labour and the evaluated adverse perinatal outcomes. More specifically, a reduced MCA PI as well as a low CPR and CPUR and an increased mean UtA PI showed an association with the need to expedite delivery due to intrapartum fetal distress. Similarly, a high mean UtA PI MoM was related to an increased risk of abnormal cord gases at birth, composite adverse perinatal outcome and postnatal diagnosis of SGA, while a low MCA PI MoM and a high UA PI MoM were associated with an increased risk of composite adverse perinatal outcome and postnatal diagnosis of SGA. Nonetheless, the results of this research show that the predictive role of the Doppler evaluation in early labour is poor for all the considered adverse perinatal outcomes.

Placental dysfunction is the most commonly accepted etiology of impaired fetal growth (37-39,106,107), which is known to represent a major risk factor for stillbirth and poor labour outcomes. In this context, maternal and fetal Doppler abnormalities are acknowledged features of FGR (30,37,38,44,69,70,83) and can be tested for the diagnosis and the longitudinal monitoring of the growth restricted fetuses. Several data published over the last decade has demonstrated an association between abnormalities of the CPR and of the UtA Doppler and adverse events also among apparently uncomplicated pregnancies close to term (63-66,85), thus suggesting that these Doppler parameters may represent markers of failure to reach the growth potential at late gestation, which in most instances is associated with normal fetal size or can manifest as misdiagnosed fetal smallness (108).

If we assume that placental dysfunction can occur at any time during the gestation, early labour can be seen as the ideal timespan for the assessment of the placental residual function as it combines a short time (at examination)-to-delivery interval and a physiological condition of "contraction stress test" for the fetoplacental unit. On this ground, it is worth to be mentioned that within our selected cohort of women with low risk pregnancy over 7% of fetuses were eventually classified as SGA. These neonates were not excluded from our analysis as fetal smallness at late gestation is known to be frequently overlooked, even though the actual extent may vary based on local screening policies for fetal growth in the third trimester (109). Of note, in the subgroup of neonates who were eventually classified as SGA the incidence of OI due to intrapartum fetal distress was not higher compared to those with birthweight above the 10th percentile, among whom some may have been subjected to impaired placental function.

Cerebral redistribution is a common feature of hypoxic fetuses (53,56-58), and the CPR has been considered the most sensitive indicator of early hypoxia secondary to placental disfunction also among appropriately grown fetuses. The finding of an association between low CPR and OI due to intrapartum fetal distress, which we found in our research, is not novel as over the last decade this relationship has been investigated and confirmed by other research groups. Within unselected cohorts of women submitted to ultrasound assessment due to clinical indication beyond 37 weeks, Morales-Roselló et al. and Khalil et al. reported a higher incidence of OI due to intrapartum fetal distress, NICU admission, stillbirth and perinatal mortality at term in AGA fetuses showing reduced CPR (64-66,74). Another prospective study conducted on low risk women where the CPR was measured within 72 hours

from birth showed a higher rate of intrapartum fetal distress leading to OI and a lower birthweight percentile in in fetuses with CPR below 10th percentile (63), which was more recently confirmed in another prospective study from an Australian research group (72). Nevertheless, these data and others from the Fetal Medicine Foundation (110,111) demonstrated that the predictive role of the CPR as a screening tool for adverse perinatal events in uncomplicated pregnancy is poor, which is consistent with the results of our work. More specifically, when evaluating the primary outcome of the present study we confirm that a reduced CPR per se represents the Doppler parameter with the strongest relationship with the occurrence of OI due to intrapartum fetal distress, however its predictive performance is low being the sensitivity below the 70% and the PPV on or below the 30%. Of note, the timing of the patient enrollment – i.e. in early labour in between uterine contractions – has not led to an improved accuracy in the identification of cases of OI due to intrapartum fetal distress compared to previously reported data. Such finding can be explained by the fact that uterine contractions may be responsible for Doppler changes which are not limited to the MCA Doppler, therefore the reference ranges obtained from the study population do not allow an improvement in the identification of fetuses with subclinical impairment of the placental function. It is uncertain whether the use of different cut-off thresholds for the definition of "abnormal Doppler" could have led to different results.

With regards to the primary outcome of the study, in this research we demonstrate that increased UtA PI is an independent risk factor for OI due to intrapartum fetal distress. This result, which is somehow unexpected as patient enrolment did not reach the number which was supposed to be required based on the power sample

size calculation performed at interim analysis, can be interpreted in view of the small number of women with increased mean UtA PI MoM submitted to OI due to intrapartum fetal distress and in view of the higher cut-off threshold for the definition of increased UtA PI MoM in this series. To our knowledge only one retrospective study by Khalil et al. has evaluated the relationship between maternal Doppler and perinatal outcomes in AGA fetuses close to term, in which abnormal UtA Doppler PI proved to be associated with low CPR, with a significantly higher incidence of stillbirth or perinatal death as well as with postnatal diagnosis of SGA (85). Furthermore, we show that the combined model including a low CPR and a high UtA PI is associated with the highest sensitivity in the identification of cases with intrapartum fetal distress leading to obstetric intervention, however its predictive performance is limited. Of note, the model including the CPR and the UtA Doppler and that including the CPR alone performed better than the CPUR. This latter parameter, which incorporates the CPR and the UtA PI and has been recently suggested as a monitoring tool for SGA and FGR fetuses (84), has not proven to yield any benefit compared to previously described Doppler parameters within our selected cohort of low risk pregnancies in early labour.

Furthermore, we originally report an independent relationship between UtA Doppler and abnormal cord gases at birth, composite adverse perinatal outcome and postnatal diagnosis of SGA, however the prediction of such adverse outcomes by UtA Doppler alone or combined with other parameters proved to be poor. Based on the assumption that abnormal findings can identify those pregnancies at risk of "placental syndromes" such as preeclampsia and FGR, particularly in their most severe and early-onset forms, UtA Doppler has been extensively investigated in

women at risk of adverse outcomes and particularly in the first and in the second trimesters (112-114). Over the last decade, more data on the association between UtA Doppler assessment in the third trimester and pregnancy outcome has emerged (115-117). The association between abnormal UtA Doppler in the third trimester and the postnatal diagnosis of SGA was first reported by Maroni et al. (118) on a cohort of 66 women submitted to ultrasound assessment of the fetal growth at 34 weeks. An over three-fold higher incidence of SGA in women with apparently uncomplicated pregnancy close to term and abnormal UtA Doppler was also demonstrated in the study by Khalil et al. (85), however this research was conducted on a population of women submitted to prenatal ultrasound for clinical indication. To our knowledge our data has provided the first prospective evidence that UtA PI >95th percentile is associated with the postnatal diagnosis of fetal smallness in women with low risk pregnancy at term gestation. If we assume that placental function represents a continuum and can decline at any time throughout gestation, then our data suggest that such subclinical impairment leading to fetal hypoxia and cerebral redistribution can be identified in early labour not only by means of the CPR but also through the UtA Doppler assessment. On this ground, it is not surprising that the linear relationship between mean UtA PI MoM and CPR MoM showed a correlation between an increased impedance of the uterine arteries and the evidence of cerebral redistribution.

Finally, our data demonstrates an association between UA and middle MCA Doppler with adverse perinatal outcomes. This is not surprising as, again, abnormalities of the UA and of the MCA Doppler are among the acknowledged features of fetuses who have failed to reach their growth potential (30). However,

the UA PI is known to be within the normal range in most late-FGR fetuses (119), while the clinical role of the reduced MCA PI in normally grown fetuses is yet to be investigated to date. Of note, the models including the UA and the MCA PI yielded a poor performance in the prediction of composite adverse perinatal outcomes as well as fetal smallness at birth.

The primary aim of this prospective observational study was to investigate whether the CPR, the UtA PI or other Doppler parameters can predict the occurrence OI due to suspected intrapartum fetal distress and the occurrence of adverse perinatal outcome among uneventful term pregnancies in early stages of spontaneous labour. Our results show that the early labour assessment of maternal and fetal Doppler in a non-SGA cohort at term gestation is associated with modest sensitivity and PPV for adverse perinatal events, hence unlikely to support clinicians in the triage of apparently AGA fetuses who have failed to reach their growth potential. Such finding holds true for isolated Doppler parameters as well as for the variable combination of UtA and fetal Doppler. It is uncertain whether the prediction of adverse perinatal outcomes could be improved by models incorporating additional clinical parameters or biomarkers. Over the last decades the study of maternal cardiovascular function under normal and pathological conditions has gained much popularity (120,121). The recent advent of automated or semi-automated devices (122-124) has further supported the development of this research field as they allow a thorough evaluation of the maternal haemodynamics with no need to perform echocardiography, which still remains the gold standard reference. Under normal circumstances pregnancy is characterized by a longitudinal increase of the cardiac output (CO) and a concomitant reduction of the systemic vascular resistance (SVR).

Low CO and high SVR are considered the haemodynamic surrogates of abnormal cardiovascular adaptation to the pregnancy with placental underperfusion (125) leading to FGR and preeclampsia. However, it is yet to be investigated whether maternal haemodynamics may play a role in the prediction of adverse outcomes within the context of fetal smallness and also in appropriately grown fetuses close to term.

Similarly, the use of biomarkers of impaired placentation (i.e. sFLT, PlGF and their ratio), which has recently been evaluated in a prospective observational study including over 19000 pregnancies between 35^{+0} and 36^{+6} weeks of gestation, has not proved to yield a significant improvement in the prediction of adverse perinatal outcomes in SGA as well as in appropriately grown fetuses (14). Again, these results need to be interpreted with caution as the sFLT and the PlGF were tested remotely from delivery, which may negatively impact on their capability to identify conditions of subclinical impairment of the placental function arising close to term.

The prospective design of the study, in which the clinical management was performed by clinicians blinded to the Doppler findings, the large number of patients enrolled and the strict criteria for the study inclusion represent the major strengths of this research. Furthermore, over 50% of the cases were recruited by one single examiner across two institutions, and overall four researchers (two per units) were involved in the data collection in the two other participating centres.

On the other hand, we acknowledge that the multicentre data collection may represent a limitation as labour ward practice may differ across institutions. Within this context, the primary outcome of the study – i.e. obstetric intervention due to

intrapartum fetal distress – is subjectively defined based on a test (i.e. the CTG) whose accuracy is acknowledged to be limited by a significant number of false positives (15). Furthermore, the threshold for intervention based on CTG findings may vary based on the adoption of different guidelines for the CTG interpretation (98,126-128). A sub-analysis evaluating the differences in the caesarean section and the vacuum delivery rate for intrapartum fetal distress across the participating Units was not performed, as we believe it is beyond the purposes of the present study. Of note, the incidence of obstetric intervention due to intrapartum fetal distress may be subjected to longitudinal variations even within the context of a single institution as a result of training or audit policies which can be conducted with the aim of improving the labour ward practice (129,130).

In conclusion, our research conducted on a selected cohort of women with low risk pregnancy submitted to Doppler assessment in early active phase of the spontaneous labour shows that either isolated or combined maternal and fetal Doppler represent poor predictors of adverse perinatal outcomes. On this basis, the identification of low risk pregnancies at increased risk of intrapartum complications as a result of a subclinical impairment of the placental function still remains an unresolved issue. Further research is needed in order to evaluate whether the addition of haemodynamic parameters or biomarkers may improve the prediction of intrapartum distress in normally grown fetuses.

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