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Running Head: Outcome prediction at diagnosis of late FGR

Keywords: uterine artery Doppler, cerebroplacental ratio, umbilical artery Doppler, perinatal complications, elective delivery.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.23714

Contribution

What are the novel findings of this work?

Our data shows that at the time of the diagnosis of late-onset FGR the EFW percentile is the only ultrasound parameter independently associated with adverse perinatal outcomes including prematurity and its potentially related complications, while abnormal UtA Doppler is associated with intrapartum fetal distress leading to obstetric intervention.

What are the clinical implications of this work?

In this cohort study including non-anomalous singleton pregnancies defined as late-onset FGR according to the study inclusion criteria, we report a low frequency of maternal, perinatal and postnatal complications. Our data can be used for the antenatal counselling of the prospective parents.

Abstract

Background

Abnormal umbilical, cerebral and uterine artery Doppler findings and fetal biometry below the 3rd percentile have been proposed as risk factors for perinatal complications in late-onset fetal growth restriction (FGR). Recent evidence has allowed to reach a consensus on the clinical use of Doppler ultrasound for the monitoring and timing of delivery in early-onset FGR, however there is limited data on the relationship between abnormal Doppler and severity of the growth restriction and adverse outcome when a diagnosis of late-onset FGR is made.

Objective

To evaluate the relationship between the ultrasound parameters measured at diagnosis and perinatal adverse outcome within a cohort of late-onset FGR fetuses.

Methods

This is a multicentre retrospective study between 2014 and 2019 including non-anomalous singleton pregnancies complicated by late-onset FGR, which was defined either by abdominal circumference (AC), estimated fetal weight (EFW) <10th percentile for the gestation or by a reduction of the longitudinal growth of the AC by over 50 percentiles compared to an ultrasound scan performed between 18 and 32 weeks of gestation. Sonographic findings at diagnosis were compared between fetuses with and without adverse outcomes including stillbirth, obstetric intervention due to intrapartum distress, neonatal acidaemia, transfer to neonatal intensive care unit (NICU) and composite adverse perinatal outcome (CAO), which was defined by either stillbirth or the combination of at least two adverse perinatal outcomes.

Results

Overall, 468 cases with full biometry and umbilical, middle cerebral, and uterine artery (UtA) Doppler data were included, among whom CAO was recorded in 53 (11.3%). At logistic regression analysis, only the EFW percentile proved to be independently associated with CAO (p=0.01) and NICU admission (p<0.01), while the mean UtA pulsatility index (PI) MoM >95th percentile at diagnosis proved to be independently associated with obstetric intervention due to intrapartum distress (p<0.01). The model including baseline pregnancy characteristics and the EFW percentile was associated with an area under the curve of 0.889, 95%CI (0.813-0.966), p<0.001 for CAO. A cut-off value corresponding to the 3.95th percentile was found to better discriminate between cases with and without CAO yielding a 58.5% sensitivity [95% confidence interval (CI) (44.1-71.9)], a 69.6% specificity [95%CI (65.0-74.0)], a 19.8% positive predictive value [95%CI (13.8-26.8)], and a 92.9% negative predictive value [95%CI (89.5-95.5)].

Conclusions

Retrospective data on a large cohort of late-onset FGR fetuses shows that at diagnosis the EFW is the only sonographic parameter independently associated with the occurrence of adverse perinatal outcomes, while a mean UtA PI MoM >95th percentile at diagnosis is independently associated with intrapartum distress leading to obstetric intervention.

Introduction

Fetal growth restriction (FGR) is a complex and multifactorial disorder affecting fetal development that complicates approximately 10% of all pregnancies. FGR currently represents one of the leading causes of perinatal mortality and morbidity including iatrogenic preterm delivery[1,2]. It is also known to be associated with an increased risk of suboptimal neurodevelopmental outcome[3] and long-term disease including cardiovascular morbidity[4,5].

According to the Delphi consensus criteria, FGR is differentiated into an early and late-onset phenotype depending on whether it is identified before or after 32 weeks gestational age[6]. Uteroplacental insufficiency is acknowledged to represent the major determinant of impaired fetal growth across gestation[7-9], however available evidence has shown that early-onset and late-onset FGR are characterized by a different clinical behaviour. The former is a rare condition commonly associated with hypertensive disorders of the pregnancy (HDP) and a high risk of delivery at gestational age remote from term[10-13], and the latter is more common but difficult to discriminate from non-pathological smallness[14].

There is no effective treatment to reverse the course of FGR except delivery. However, while evidence for the management of FGR between 26 and 32 weeks has emerged from the TRUFFLE study[10-13], to date there is no "grade A" evidence supporting the monitoring strategy and the timing of delivery in late-onset FGR. Furthermore, there is limited data on the occurrence of perinatal complications when a diagnosis of late-onset FGR is made. In such context, great interest has arisen towards the quantitative evaluation of the estimated fetal weight (EFW)[15] as well as in the Doppler assessment of the fetal hemodynamic response to hypoxemia, which can be evaluated by means of the cerebro-placental ratio (CPR) or the umbilical-to-cerebral ratio (UCR), and of the placental impedance to uterine perfusion, which can be assessed by measuring the uterine artery (UtA) Doppler.

Several studies have demonstrated a relationship between the sonographic indicators of placental insufficiency, cerebral blood flow redistribution and adverse perinatal outcome in late-onset FGR[16-20]. Furthermore, isolated severe FGR – i.e. an abdominal circumference (AC) or an EFW <3rd percentile – has also been proposed as an additional risk factor for fetal or neonatal complications[21-23]. On this ground, the latest and widely agreed definition of late-onset FGR includes not only a biometric percentile threshold, but also the sonographic indicators of reduced longitudinal growth and of cerebral redistribution[6].

The recently published data of the prospective observational feasibility study conducted by the TRUFFLE group has led to the identification of the thresholds for umbilical and cerebral Doppler values which most strongly correlate with adverse outcome[16]. Such cut-off values are being evaluated in a randomized controlled trial investigating the role of the Doppler assessment of the UCR in the monitoring and timing of delivery in late-onset FGR[16,24] in which late-onset FGR is defined by means of either an EFW or an AC <10th percentile or by means of an abdominal circumference decreased by 50 percentiles since an ultrasound scan at 18-32 weeks. By using the same diagnostic criteria adopted by the TRUFFLE group, in this study we aimed to evaluate the relationship between the Doppler and biometry ultrasound parameters measured at diagnosis and adverse outcome at birth within a selected cohort of late-onset FGR fetuses.

Methods

This was a retrospective study conducted at three tertiary academic units in Italy (University of Parma, University of Florence, and University of Trieste), and including a consecutive series of non-anomalous singleton pregnancies referred for expert ultrasound between 32^{+0} and 36^{+6} weeks of gestation due to suspected FGR from January 2014 to December 2019. All the pregnancies were dated based on the first-trimester crown–rump length.

All non-anomalous singleton pregnancies referred between 32^{+0} and 36^{+6} weeks of gestation due to suspected FGR were screened. A diagnosis of late-onset FGR was made on the basis of an EFW or an AC <10^{th} percentile or on a decrease of the AC >50 percentiles from ultrasound scan performed between 18 and 32 weeks. For each pregnant woman, information concerning fetal biometry and maternal (i.e. mean UtA pulsatility index (PI)) and fetal (i.e. umbilical artery (UA) PI, middle cerebral artery (MCA) PI, and their ratio CPR) Doppler assessment at diagnosis was recorded. The EFW was computed by means of the Hadlock IV formula[25], while the Doppler assessment was performed following the recommendations by the International Society of Ultrasound in Obstetrics and Gynecology[26]. In order to adjust for the gestational age, the EFW percentile was considered, while the Doppler parameters were converted into multiples of the median (MoMs).

Cases were excluded in the event of missing data concerning the UA, the MCA and the UtA Doppler at the time of the diagnosis of late-onset FGR, the perinatal outcome, and the postnatal diagnosis of malformations, chromosomal abnormalities or genetic syndromes and congenital infections.

As per management protocol, which was consistent in the three participating centres, follow-up scans were arranged every two weeks in the absence of signs of cerebral redistribution, defined as CPR >5^{th} percentile, on a weekly basis in the case of CPR <5^{th} percentile or of UtA PI >95^{th} percentile and on alternate days in the case of UA PI >95^{th} percentile. Induction of labour was recommended between 36 and 37 weeks of gestation in the case of UA PI >95^{th} percentile, at 37 weeks in the case

of EFW or AC <3rd percentile, between 37 and 38 weeks if signs of redistribution were noted (i.e. CPR <5th percentile), and 39-40 weeks in the absence of any of such risk factors for adverse perinatal outcome. The monitoring strategy included also cardiotocography (CTG), which was performed at each assessment. The finding of UA absent or reversed end-diastolic flow (AREDF) and spontaneous repetitive decelerations on CTG represented indications for immediate delivery by caesarean section. Antenatal steroids for lung maturation were administered in all cases delivering before 34^{+6} weeks[27]. Pre-eclampsia represented an indication for delivery at 37 weeks or at 34 weeks in the presence of clinical signs of severity of the disease[28].

In all cases submitted to labour induction, cervical ripening was promoted either by means of a cervical ripening balloon or by means of the vaginal administration of a slow-release prostaglandin E2 pessary, which was followed by oxytocin infusion if the onset of labour did not occur. Caesarean section was electively performed in the presence of UA AREDF, or spontaneous repetitive decelerations on CTG monitoring, or for other obstetric indications. The clinicians responsible for the intrapartum care were not blinded to the antepartum findings. The diagnosis of intrapartum fetal distress was defined by the physician in charge for the patient care based on abnormal CTG tracing according to the FIGO classification system[29]. As per standard practice, the paired analysis of the cord gases was performed at birth according to the recommendations by the American College of Obstetricians and Gynecologysts[30].

Information concerning maternal demographics, peripartum and neonatal outcomes were collected from patient case notes. Neonatal outcome was assessed by examining birthweight and birthweight centile corrected for gender[31], cord arterial pH and base excess at delivery, Apgar score at 5 minutes, need for resuscitation at birth, need for respiratory support at birth, neonatal jaundice (as defined by serum bilirubin above 20.6mg/dL [350umol/L])), neonatal hypoglycaemia (defined by 2

consecutive whole blood glucose by glucometer or 1 plasma glucose <3.3 mMol/L), need for admission to neonatal intensive care unit (NICU), and length of neonatal admission.

The primary aim of the study was to evaluate the relationship between the sonographic parameters measured at diagnosis and the occurrence of composite adverse perinatal outcome (CAO), as defined by the combination of either stillbirth or at least two among the following: obstetric intervention due to intrapartum fetal distress, neonatal acidaemia as defined by UA pH <7.10[32], birthweight <3rd centile, and transfer to NICU. Additionally, neonatal hypoglycaemia, as defined by 2 consecutive whole blood glucose by glucometer or 1 plasma glucose <3.3 mMol/L[33], neonatal hyperbilirubinemia/jaundice, as defined by serum bilirubin above 20.6 mg/dL (350 µmol/L)[34], need for respiratory support at birth, and the length of neonatal admission were evaluated.

Ethics approval for this study was granted by the local ethics committee in all the involved centres.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Inc., Armonk, NY, USA). Data were shown as mean $\pm$ standard deviation or as number (percentage). Categorical variables were compared using the Chi-square or Fisher's exact test. Comparison of continuous variables included T test for independent sample and 2-tailed *t* tests. Logistic regression analysis was used to control for potential confounding variables, and receiver operating characteristic (ROC) curve analysis was performed in order to evaluate the accuracy in the prediction of the primary outcome. The method of DeLong et al. was used for the comparison of the ROC curves[35]. P <0.05 was considered as statistically significant. This study was conducted following the STROBE guidelines[36].

Results

Overall, 679 cases (253 from the University of Parma, 258 from the University of Florence, and 168 from the University of Trieste) defined as late-onset FGR according to the study inclusion criteria were retrieved, among whom 468 were included for the data analysis following the evaluation of the exclusion criteria (Figure 1). The demographic features and the perinatal outcomes of the included cases are summarized in Table 1. One case of stillbirth was recorded. Obstetric intervention due to intrapartum distress was performed in 41 cases, which accounted for 8.8% of all deliveries and 11.6% of the deliveries when elective caesarean sections were excluded. Over 60% of the neonates had birthweight <10th percentile, with no difference in terms of adverse outcomes between those weighing above or below the 10th percentile threshold (Supplementary Table 1). Neonatal acidaemia, NICU admission, and composite adverse perinatal outcome were recorded in 6 (1.7%), 108 (23.1%), and 53 (11.3%) cases, respectively, while neonatal hypoglycaemia and need for respiratory support at birth were recorded in 91 (19.4%) and 32 (6.8%) cases, respectively (Table 1).

The results of logistic regression analysis evaluating the association between antenatal factors and perinatal outcomes are shown in Table 2. The EFW percentile at diagnosis and the gestational age at delivery proved to be independently associated with the occurrence of CAO (p=0.01 and p<0.01, respectively) (Table 2a) and NICU admission (p<0.01 for both) (Table 2b), while the mean UtA PI MoM >95th percentile at diagnosis was independently associated with obstetric intervention due to intrapartum fetal distress (p=0.01) (Table 2c). When evaluating the baseline risk for CAO by means of logistic regression analysis and a model including maternal age, booking BMI, ethnicity, parity, smoking status, the presence of comorbidities and the gestational age at the US examination (pre-test probability), only the addition of the EFW percentile at diagnosis resulted in a significant

increase in the area under the curve (0.889, 95%CI [0.813-0.966] vs 0.803, 95%CI [0.719-0.886], p=0.02) (Figure 2).

An EFW cut-off value corresponding to the 3.95th percentile was found to better discriminate between cases with and without CAO. An EFW <3.95th percentile at diagnosis was associated with an almost three-times higher incidence of CAO (19.7% vs 7.1%, p<0.01), an over two-fold higher rate of NICU admission (38.5% vs 15.4%, p<0.01), an almost two-fold higher incidence of neonatal hypoglycaemia (27.3% vs 15.4%, p<0.01). Furthermore, an EFW below the cut-off value of the 3.95th percentile was associated with an increased rate of caesarean section (48.4% vs 27.7%, p<0.01) and of obstetric intervention due to intrapartum fetal distress (12.7% vs 6.8%, p=0.03) as well as an over two-fold higher frequency of delivery prior to 37 weeks of gestation (24.2% vs 10.3%, p<0.01), and a longer neonatal hospitalization (6 [2 – 42] days vs 3 [1 – 37], p<0.01) (Table 3). Overall, an EFW <3.95th percentile at diagnosis proved to be a poor predictor of CAO yielding a 58.5% sensitivity [95%CI (44.1-71.9)], a 69.6% specificity [95%CI (65.0-74.0)], a 19.8% PPV [95%CI (13.8-26.8)], and a 92.9% NPV [95%CI (89.5-95.5)].

Approximately one third (162/468, 34.6%) of the included cases met the Delphi diagnostic criteria for late-onset FGR. Such cases showed an increased frequency of mean UtA PI MoM >95th percentile (29.6% vs 16.0%, p<0.01), preterm delivery prior to 37 weeks (25.9% vs 9.2%, p<0.01) and obstetric intervention (46.9% vs 32.1%, p<0.01) as well as an earlier gestational age at delivery ($37^{+4}\pm1^{+3}$ vs $38^{+5}\pm1^{+3}$, p<0.01) and a lower 5 minutes Apgar (p<0.01) compared to the cases non fulfilling the Delphi diagnostic criteria for late-onset FGR. Furthermore, late-onset FGR fetuses as defined according to the Delphi criteria showed an increased incidence of perinatal adverse outcome including NICU admission (34.2% vs 17.3%, p<0.01), need for respiratory support at birth (13.0% vs 3.6%, p<0.01) and CAO (17.9% vs 7.8%, p<0.01) as well as a longer neonatal hospitalization (5 (2 – 42) vs 3 (1 – 37) days, p<0.01) (Supplementary Table 2).

Discussion

In this cohort study including non-anomalous singleton pregnancies defined as late-onset FGR according to the study inclusion criteria, we report a low frequency of maternal, perinatal and postnatal complications. Our data also shows that the EFW percentile at the time of the diagnosis of late-onset FGR is the only ultrasound parameter independently associated with adverse perinatal outcomes including prematurity and its potentially related complications in terms of NICU admission, neonatal hypoglycaemia and length of neonatal admission. Of note, also the frequency of caesarean section and obstetric intervention due to intrapartum fetal distress was shown to be almost two-fold higher among the fetuses with the EFW percentile below the 3.95th percentile. Such a finding is consistent with previous studies demonstrating a correlation between the risk of poor neonatal outcomes including stillbirth and the actual EFW[21-23]. More specifically, the risk of adverse outcomes is acknowledged to exponentially increase with decreasing EFW percentile[23]. Furthermore, our results demonstrate an independent association between an abnormally raised mean UtA PI and obstetric intervention due to intrapartum fetal distress.

Unexpectedly, a CPR <5th percentile or a mean UtA PI >95th percentile at diagnosis did not prove to be independently associated with the occurrence of the primary outcome of the study. The finding of either Doppler indicators of cerebral redistribution or abnormalities of the UtA Doppler have been advocated as surrogate of clinical severity in the context of subclinical impairment of the placental function. On this basis, such parameters have been suggested to represent indications for anticipated delivery in the context of antenatally detected FGR[21,22]. According to the recently published guidelines by the International Society of Ultrasound in Obstetrics and Gynecology the use of the CPR is endorsed in late-onset FGR, while the assessment of the UtA Doppler is not recommended for the monitoring nor to time delivery when a diagnosis of FGR is made[14]. Nonetheless, the results from this present study and those reported by other research groups[20,21]

support the concept that abnormalities in the UtA Doppler per se represent a risk factor for perinatal complications in the context of antenatally suspected FGR.

Several studies have demonstrated an association between a reduced CPR and adverse outcomes including stillbirth in fetuses with an EFW below the 10th percentile[14,21,22,37-40]. The recently published findings of the TRUFFLE feasibility study demonstrated an association between composite adverse outcome and abnormal CPR close to delivery[16]. Consistent with that data, in this study we report an increased frequency of fetal – but also maternal – Doppler abnormalities with increasing severity of the growth restriction. However, in our cohort we report a lack of association between CAO and Doppler abnormalities at diagnosis. Such unexpected finding could have resulted from the evaluation of the Doppler parameters at diagnosis rather than close to delivery. While little or no data exists on longitudinal trends of maternal and fetal Doppler in late-onset FGR[17,18], two recently published studies support the concept of a progression of the Doppler indicators of placental insufficiency across gestation in fetuses with an EFW below the 10th percentile[16,41]. A recent prospective study found a relationship between CPR and UtA Doppler abnormalities at diagnosis of late-onset FGR and adverse outcome, however it has to be acknowledged that the criteria for the definition of FGR are not consistent with those adopted in this present study[42]. The concept that the diagnostic criteria impact on the occurrence of adverse outcome is not novel[43], and is further supported by the sub-analysis comparing the outcome of the fetuses who met vs those not fulfilling the Delphi diagnostic criteria for late-onset FGR.

When looking at the other perinatal and neonatal outcomes, our data discloses an incidence of NICU admission just above 1 in 5 cases, which is consistent with that reported in the studies by Figueras et al.[21] and Madden et al.[44]. Prematurity, which has been recorded in just less than one fifth of the cases included in our cohort, is known to be related to an increased incidence of hypoglycaemia[45]. However, more recent evidence suggests that FGR, being associated with a low body fat

composition, represents the strongest risk factor for neonatal hypoglycaemia[46,47]. The low rate of need for respiratory support at birth is consistent with that recently reported by the TRUFFLE[16] and other research groups[44], while the one-in-ten rate of hyperbilirubinemia confirms previous data reporting that FGR as well as prematurity represent independent risk factors[34].

Albeit within the limitations of the adoption of different antenatal and postnatal growth charts, the unexpected high rate of neonates with birthweight above the 10th percentile is likely to have resulted from the inclusion of the fetuses considered at risk based on the longitudinal reduction of the AC from midtrimester scan, which has been recently endorsed by the TRUFFLE group[16]. Of note, the 10th percentile birthweight threshold was not associated with an increased incidence of adverse perinatal outcomes nor with differences in terms of Doppler abnormalities at diagnosis. The findings from a recent retrospective study by Meler et al. show that an EFW below the 10th percentile in the absence of the criteria of severity (i.e. fetal size below the 3rd percentile or abnormalities of the CPR or the UtA Doppler) results in perinatal outcomes comparable to normally grown neonates[41]. In our cohort, no comparison could be undertaken between the fetuses identified as FGR and those normally grown, however our results support the concept that the absence of criteria of severity is associated with improved perinatal outcome in the context of FGR.

To our knowledge this is the first study providing information on the perinatal outcomes of late-onset FGR based on the sonographic findings at diagnosis. The main strength of this study is represented by the large number of included cases together with its multicentre design involving three referral academic units. Of note, the participating centres had similar protocols for the antenatal and perinatal management of late-onset FGR.

On the other hand, the retrospective design is acknowledged as the major limitation of the study. Less than one third of the cases identified as late-onset FGR were excluded due to incomplete/missing outcomes. Another limitation is represented by the fact that there is no data

concerning the indication for delivery other than for late-onset FGR. More specifically, we report a low incidence of HDP, diabetes mellitus/gestational diabetes and autoimmune disorders potentially indicating anticipated delivery, however we could not retrieve information on their co-existence nor on the occurrence of early delivery only for maternal indication. The antenatal care of growth restricted fetuses may be complicated by HDP[10-13], however there is a paucity of data on the occurrence of HDP in the context of pregnancies complicated by late-onset FGR[16,48]. Another limitation is that no information on longitudinal growth and Doppler up to delivery was considered for this present study. Furthermore, different growth charts were adopted in the participating units. The choice of the growth chart impacts on the identification of late-onset FGR, and we previously reported on the discrepancy in the growth charts adopted across different referral units in Italy[49]. Finally, cases were managed according to clinical and ultrasound parameters in the context of locally adopted protocols, which may account for a source of bias. Therefore, it has to be acknowledged that no recommendations can be made based on the findings of this present study.

In conclusion, this study reports the maternal and perinatal outcomes of a selected cohort of late-onset FGR fetuses identified on the basis of a biometry cut-off or longitudinal growth criteria. While we report a low incidence of adverse perinatal events, we demonstrate that when late-onset FGR is diagnosed the EFW percentile represents the only sonographic parameter associated with composite adverse outcome and that abnormal UtA Doppler is associated with intrapartum fetal distress leading to obstetric intervention. These data can be used for the antenatal counselling of the prospective parents.

Acknowledgments

None.

Conflict of interest statement

All the Authors state no conflict of interest and nor financial disclosures related to this work.

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Figure Legends

Figure 1 – Flow chart (according to STROBE guidelines)36 for inclusion of cases.

Figure 2 – Receiver operating characteristic curve analysis showing the area under the curve for composite adverse outcome of the baseline antenatal risk alone and associated with the estimated fetal weight at diagnosis.

Supplementary Information

Supplementary Table 1 – Maternal demographics, clinical characteristics and perinatal outcomes in neonates with and without birthweight <10th percentile.

Supplementary Table 2 – Maternal demographics, clinical characteristics and perinatal outcomes in fetuses fulfilling the Delphi diagnostic criteria for late-onset fetal growth restriction (FGR) at diagnosis vs those not fulfilling the Delphi diagnostic criteria for late-onset FGR at diagnosis.

Table 1 – Demographic features and intrapartum and perinatal outcomes of the included cases. (n=468 unless otherwise stated)

Maternal age, years ***Mean ± SD***	32.6 ± 5.7
Booking BMI, kg/m² ***Mean ± SD***	22.1 ± 4.1
BMI at delivery, kg/m² ***Mean ± SD***	26.3 ± 4.3
Ethnicity ***n (%)***	Caucasian 402/468 (85.9%) African 20/468 (4.3%) Asian 32/468 (6.8%) Other 14/468 (3.0%)
Parity ***n (%)***	Nulliparous 328/468 (70.1%)
Smoking ***n (%)***	Smokers 48/468 (10.3%)
Comorbidity ***n (%)***	HDP 28/468 (6.0%) DM/GDM 30/468 (6.4%) Autoimmune disorders 19/468 (4.1%)
Gestation at diagnosis, weeks^{+days} ***Mean ± SD***	$34^{+2} \pm 1^{+4}$
Gestation at delivery, weeks^{+days} ***Mean ± SD***	$38^{+2} \pm 1^{+4}$
Delivery <37 weeks ***n (%)***	70/468 (15.0%)
Delivery <34 weeks ***n (%)***	6/468 (1.3%)
Mode of delivery ***n (%)***	SVD 294/468 (62.8%) ID due to suspected IFD 5/468 (1.1%) CS due to suspected IFD 36/468 (7.7%) EICS due to IUGR 38/468 (8.1%) EICS non IUGR 78/468 (16.7%) ID due to dystocia 7/468 (1.5%) CS due to dystocia 10/468 (2.1%)
Neonatal gender ***n (%)***	Male 217/468 (46.4%)
Birthweight, grams ***Mean ± SD***	2489 ± 420
Birthweight percentile ***Mean ± SD***	10.0 ± 11.6
Birthweight <10th centile ***n (%)***	294/468 (62.8%)
Birthweight <3rd centile ***n (%)***	136/468 (29.1%)
Birthweight <1st centile ***n (%)***	34 (7.3%)
Umbilical artery pH	7.29 ± 0.08

Mean ± SD ***n=363***	
Umbilical artery pH <7.10 ***n (%)*** ***n=363***	6/363 (1.7%)
Apgar at 5 minutes ***Median (range)***	9 (7 – 10)
Apgar <7 at 5 minutes ***n (%)***	0/468 (0.0%)
Stillbirth ***n (%)***	1/468 (0.2%)
NICU admission ***n (%)***	108/468 (23.1%)
Need for respiratory support at birth ***n (%)***	32/468 (6.8%)
Neonatal jaundice ***n (%)***	81/468 (17.3%)
Neonatal hypoglycaemia ***n (%)***	91/468 (19.4%)
Composite adverse perinatal outcome* ***n (%)***	53/468 (11.3%)
Length of neonatal hospitalization, days ***Median (range)***	4 (1 – 42)

SD: standard deviation

EICS: elective caesarean section

SVD: spontaneous vaginal delivery

ID: instrumental delivery

CS: caesarean section

IFD: intrapartum fetal distress

HDP: hypertensive disorder of the pregnancy

DM: diabetes mellitus

GDM: gestational diabetes mellitus

NICU: neonatal intensive care unit

*Defined by either stillbirth or a combination of two among obstetric intervention due to intrapartum fetal distress, neonatal acidaemia (UA pH <7.10), birthweight <3rd centile and transfer to neonatal intensive care unit.

Table 2 – Multivariable logistic regression analysis of association of demographic, sonographic and antenatal parameters with a) the occurrence of composite adverse perinatal outcome (CAO), b) the occurrence of neonatal intensive care unit (NICU) admission and c) obstetric intervention due to intrapartum fetal distress.

a)

	CAO	
	Value, 95% confidence interval	***p***
EFW percentile at diagnosis	0.631, 95%CI (0.440-0.904)	0.01
UA PI >95th percentile at diagnosis	0.707, 95%CI (0.076-6.563)	0.76
CPR <5th percentile at diagnosis	1.191, 95%CI (0.163-8.697)	0.86
Mean UtA PI >95th percentile at diagnosis	1.445, 95%CI (0.284-7.344)	0.66
Maternal age	1.063, 95%CI (0.943-1.198)	0.32
Ethnicity	1.209, 95%CI (0.278-5.252)	0.80
Booking BMI	0.901, 95%CI (0.609-1.333)	0.60
Term pregnancy BMI	1.153, 95%CI (0.779-1.708)	0.48
Parity	1.215, 95%CI (0.229-6.443)	0.82
Smoking	2.926, 95%CI (0.444-19.272)	0.26
Comorbidities*	0.745, 95%CI (0.136-4.082)	0.73
Gestational age at delivery	0.477, 95%CI (0.278-0.816)	<0.01

b)

	NICU admission	
	Value, 95% confidence interval	***p***
EFW percentile at diagnosis	0.695, 95%CI (0.542-0.890)	<0.01
UA PI >95th percentile at diagnosis	0.897, 95%CI (0.144-5.598)	0.91
CPR <5th percentile at diagnosis	0.738, 95%CI (0.155-3.521)	0.70
Mean UtA PI >95th percentile at diagnosis	1.612, 95%CI (0.472-5.507)	0.45
Maternal age	0.989, 95%CI (0.899-1.087)	0.82
Ethnicity	0.858, 95%CI (0.161-4.563)	0.86
Booking BMI	1.055, 95%CI (0.830-1.342)	0.66
Term pregnancy BMI	0.949, 95%CI (0.753-1.196)	0.66
Parity	0.528, 95%CI (0.147-1.899)	0.33
Smoking	0.754, 95%CI (0.148-3.833)	0.73
Comorbidities*	1.342, 95%CI (0.377-4.776)	0.65
Gestational age at delivery	0.327, 95%CI (0.200-0.535)	<0.01

c)

	Obstetric intervention due to intrapartum fetal distress	
	Value, 95% confidence interval	***p***
EFW percentile at diagnosis	0.992, 95%CI (0.879-1.121)	0.90
UA PI >95th percentile at diagnosis	1.397, 95%CI (0.282-6.922)	0.68
CPR <5th percentile at diagnosis	0.598, 95%CI (0.127-2.811)	0.52
Mean UtA PI >95th percentile at diagnosis	4.373, 95%CI (1.429-13.385)	0.01
Maternal age	0.981, 95%CI (0.901-1.068)	0.67
Ethnicity	0.223, 95%CI (0.026-1.946)	0.18
Booking BMI	0.908, 95%CI (0.704-1.171)	0.46
Term pregnancy BMI	1.174, 95%CI (0.917-1.502)	0.20
Parity	0.859, 95%CI (0.281-2.619)	0.79
Smoking	0.581, 95%CI (0.107-3.147)	0.53
Comorbidities*	0.401, 95%CI (0.088-1.820)	0.24
Gestational age at delivery	0.767, 95%CI (0.526-1.118)	0.17

*presence of either among hypertensive disorders of the pregnancy, diabetes mellitus/gestational diabetes or autoimmune disorders.

EFW: estimated fetal weight

UA PI: pulsatility index of umbilical artery

CPR: cerebro-placental ratio

UtA PI: uterine artery pulsatility index

BMI: body mass index

Table 3 – Maternal demographics, clinical characteristics and perinatal outcomes according to the estimated fetal weight percentile at diagnosis.

	EFW <3.95 percentile N 157	***EFW ≥3.95 percentile N 311***	***p***
Maternal age, years Mean ± SD	32.9 ± 6.0	32.4 ± 5.6	0.46
Booking BMI, kg/m² ***Mean ± SD***	22.0 ± 4.1	22.2 ± 4.1	0.74
BMI at delivery, kg/m² ***Mean ± SD***	26.1 ± 4.8	26.4 ± 4.1	0.71
Ethnicity n (%)	Caucasian 139/137 (88.5%) African 4/137 (2.5%) Asian 11/137 (7.0%) Other 3/137 (2.0%)	Caucasian 263/311 (84.6%) African 16/311 (5.1%) Asian 21/311 (6.8%) Other 11/311 (3.5%)	0.43
Parity n (%)	Nulliparous 113/157 (72.0%)	Nulliparous 215/311 (69.1%)	0.53
Smoking n (%)	Smokers 18/157 (11.5%)	Smokers 30/311 (9.6%)	0.54
Comorbidity n (%)	HDP 9/157 (5.7%) DM/GDM 11/157 (7.0%) Autoimmune disorders 8/157 (5.1%)	HDP 19/311 (6.1%) DM/GDM 19/311 (6.1%) Autoimmune disorders 11/311 (3.5%)	0.84
Gestation at diagnosis, weeks+days ***Mean ± SD***	$34^{+1} \pm 1^{+3}$	$34^{+2} \pm 1^{+4}$	0.30
Umbilical artery PI at diagnosis >95th percentile n (%)	21/157 (13.4%)	15/311 (4.8%)	<0.01
Cerebroplacental ratio at diagnosis <5th percentile n (%)	27/157 (17.2%)	30/311 (9.6%)	0.02
Mean uterine artery PI at diagnosis >95th percentile n (%)	41/157 (26.1%)	56/311 (18.0%)	0.04
Gestation at last scan, weeks+days ***Mean ± SD***	$36^{+1} \pm 1^{+4}$	$37^{+0} \pm 1^{+5}$	<0.01
Gestation at delivery, weeks+days ***Mean ± SD***	$37^{+4} \pm 1^{+3}$	$38^{+5} \pm 1^{+3}$	<0.01
Delivery <37 weeks n (%)	38/157 (24.2%)	32/311 (10.3%)	<0.01
Delivery <34 weeks n (%)	3/157 (1.9%)	3/311 (1.0%)	0.39
Mode of delivery n (%)	SVD 78/157 (49.7%) ID 3/157 (1.9%) CS 76/157 (48.4%)	SVD 216/311 (69.5%) ID 9/311 (2.9%) CS 86/311 (27.7%)	<0.01

Obstetric intervention due to intrapartum fetal distress n (%)	20/157 (12.7%)	21/311 (6.8%)	0.03
Neonatal gender n (%)	Male 83/157 (52.9%)	Male 134/311 (43.1%)	0.05
Birthweight, grams Mean ± SD	2212 ± 387	2629 ± 364	<0.01
Birthweight percentile Mean ± SD	8.8 ± 10.1	10.7 ± 12.3	0.09
Birthweight <10th centile n (%)	103/157 (65.6%)	191/311 (61.4%)	0.38
Birthweight <3rd centile n (%)	45/157 (28.7%)	91/311 (29.3%)	0.89
Birthweight <1st centile n (%)	12/157 (7.6%)	22/311 (7.1%)	0.82
Umbilical artery pH Mean ± SD n=363	7.29 ± 0.09	7.29 ± 0.08	0.79
Umbilical artery pH <7.10 n=363	2/131 (1.5%)	4/232 (1.7%)	0.89
Apgar at 5 minutes Median (range)	9 (7 – 10)	9 (7 – 10)	<0.01
Apgar <7 at 5 minutes n (%)	0/157 (0.0%)	0/311 (0.0%)	-
NICU admission n (%)	60/157 (38.3%)	48/311 (15.4%)	<0.01
Composite adverse perinatal outcome* n (%)	31/157 (19.7%)	22/311 (7.1%)	<0.01
Need for respiratory support at birth n (%)	22/157 (14.0%)	10/311 (3.2%)	<0.01
Intubation at birth n (%)	1/157 (0.6%)	0/311 (0.0%)	0.16
Neonatal jaundice n (%)	31/157 (19.7%)	50/311 (16.1%)	0.32
Neonatal hypoglycemia n (%)	43/157 (27.3%)	48/311 (15.4%)	<0.01
Length of neonatal hospitalization, days Median (range)	6 (2 – 42)	3 (1 – 37)	<0.01

EFW: estimated fetal weight

SD: standard deviation

PI: pilsatility index

EFW: estimated fetal weight

BMI: body mass index

SVD: spontaneous vaginal delivery

ID: instrumental delivery

CS: cesarean section

HDP: hypertensive disorder of the pregnancy

DM: diabetes mellitus

GDM: gestational diabetes mellitus

*Defined by the combination of either stillbirth or at least two among obstetric intervention due to intrapartum fetal distress, neonatal acidemia (UA pH <7.10), birthweight <3rd centile and transfer to neonatal intensive care unit.

Figure 1 – Flow chart (according to STROBE guidelines)[36] for inclusion of cases.

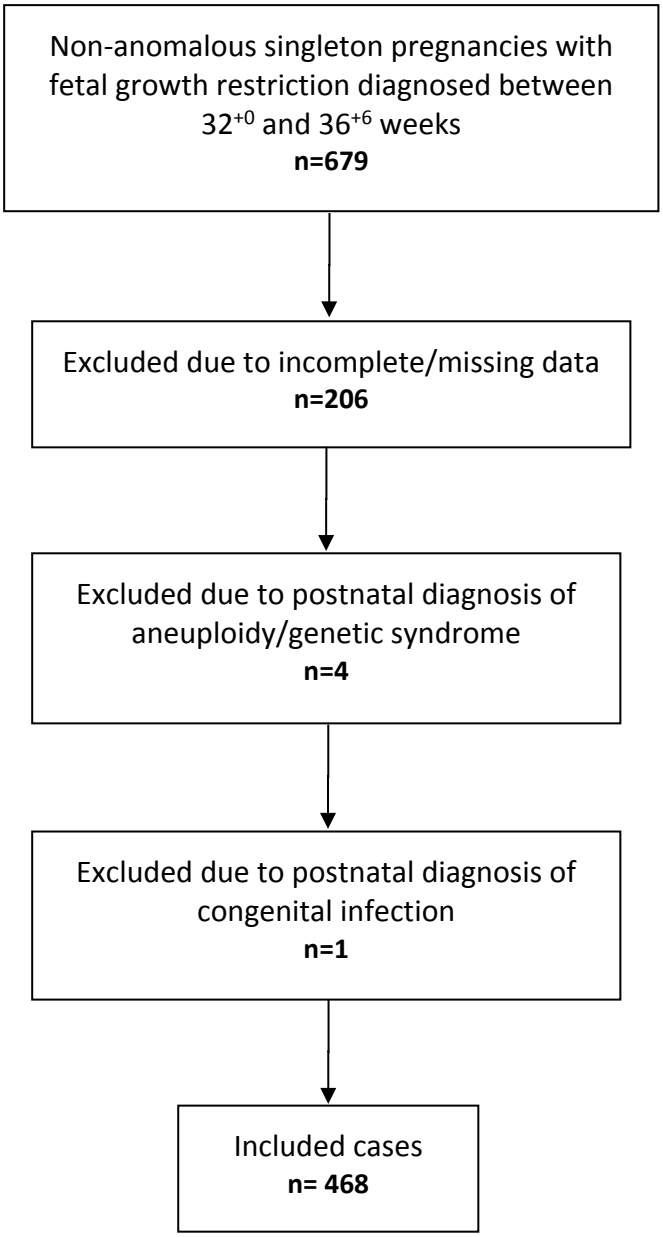

Figure 2 – Receiver operating characteristic curve analysis showing the area under the curve for composite adverse outcome of the baseline antenatal risk alone and associated with the estimated fetal weight at diagnosis.