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Tesis Doctoral

ASSESSMENT OF FETAL GROWTH AND PLACENTAL FUNCTION IN PREDICTING PERINATAL MORBIDITY AND MORTALITY

Autor

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UNIVERSIDAD DE ZARAGOZA
Escuela de Doctorado

Programa de Doctorado en Medicina

2024

Assessment of fetal growth and placental function in predicting perinatal morbidity and mortality

Submitted by

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For the degree of doctor in Medicine

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HACE CONSTAR:

Que el trabajo de investigación titulado “Assessment of fetal growth and placental function in predicting perinatal morbidity and mortality” que presenta Angelo Cavallaro, Licenciado en Medicina para optar al GRADO DE DOCTOR, fue realizado bajo mi dirección no existiendo impedimento alguno para su defensa como compendio de publicaciones.

Y para que conste a los efectos oportunos firmo el presente en Zaragoza a 4 de Diciembre 2023.

Fdo. Dr. Daniel Oros López

Profesor Titular de Obstetricia y Ginecología.

Facultad de Medicina. Universidad de Zaragoza

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Oxford, 3rd July 2023

Dr Angelo Cavallaro joined the Fetal Medicine Unit at the John Radcliffe Hospital as clinical research fellow from June 2019 to June 2020. During this time, he took active part in research activities relating to fetal growth. His work has led to improvements in the identification and management of fetal growth restriction, prevention of stillbirth, perinatal death, and hypoxic ischemic encephalopathy. He has played leading roles in the development of a new care pathway for fetal growth assessment and creation of a new service within the Fetal Medicine Unit aiming to detect fetuses at risk of stillbirth and perinatal adverse outcome.

His research experience and specialty training at the Oxford University Hospitals NHS Foundation Trust have provided him with the skills and expertise to deliver optimal care in fetal medicine, fetal cardiology, and acute obstetric care within a tertiary referral centre, with level 3 neonatal facilities. He is passionate about research and teaching to deliver evidence based and high standard care. He has been co-author of several publications in peer-reviewed journals. He has regularly presented results from his research activity in the form of oral communications at national and international conferences.

He is hard working and polite, and well-liked by staff and patients. He has effective administrative, organisational and time management skills. He is determined in ensuring that projects are completed to highest standards and in a timely manner. He is an excellent team player. As member of a research team, he is reliable, proactive and a good listener. He treats other members of the team with respect, and he is always supportive and willing to help. Angelo has shown exceptional talent and dedication in both clinical and research settings. He is a pleasure to work with and has, in a short time, become a trusted, valuable, and loved member of our team.

Prof Lawrence Impey

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Escuela de Doctorado
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En Zaragoza, a 15 Enero, 2024

Fdo.: Angelo Cavallaro

La presente Tesis Doctoral ha sido estructurada siguiendo las directrices de la normativa para la presentación de tesis doctorales como compendio de artículos, con mención de Tesis internacional, aprobada por la comisión de Doctorado de la Universidad de Zaragoza el día 25 de junio de 2020.

Los estudios que conforman esta Tesis Doctoral pertenecen a la misma línea de investigación. Los resultados obtenidos gracias a la realización de estos estudios, han aportado información relevante y novedosa sobre el tema y han sido recogidos en cinco artículos originales, publicados en diferentes revistas de amplia difusión internacional:

1. Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol. Ultrasound Obstet Gynecol. 2018 Jul; 52(1):66-71. PMID: 28600829

   Estado: Publicado

   Factor de impacto: 5.595

   Primer cuartil

2. Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2018 Oct; 52(4):494-500. PMID: 29266519

   Estado: Publicado

   Factor de impacto: 5.595

   Primer cuartil

3. Clinical phenotypes for risk stratification in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2022 Apr; 59(4):490-496. PMID: 34396614

   Estado: Publicado

   Factor de impacto: 7.1

   Primer cuartil

4. Ultrasound predictors of adverse outcome in pregnancy complicated by pre-existing and gestational diabetes. Acta Obstet Gynecol Scand. 2022 Jul; 101(7):787-793. PMID: 35441701

   Estado: Publicado

   Factor de impacto: 4.3

   Primer cuartil

5. Abnormal umbilical artery pulsatility index in appropriately grown fetuses in the early third trimester: an observational cohort study. J Matern Fetal Neonatal Med. 2022 Dec 8; 1-8. PMID: 36482725

   Estado: Publicado

   Factor de impacto: 1.8

   Cuarto cuartil

Contents

Abbreviations

SGA	Small for gestational age
IUGR	In utero growth restriction
FGR	Fetal growth restriction
LGA	Large for gestational age
AGA	Appropriate for gestational age
AC	Abdominal circumference
ACGV	Abdominal circumference growth velocity
MCA	Middle cerebral artery
UA	Umbilical artery
PI	Pulsatility index
CPR	Cerebroplacental ratio
CAO	Composite adverse outcome
BPD	Biparietal diameter
HC	Head circumference
FL	Femur length
EFW	Estimated fetal weight
CI	Confidence interval
CRL	Crown rump length
LMP	Last menstrual period
NT	Nuchal translucency

GA	Gestational age
TCD	Trans cerebellar diameter
QC	Quality control
BA plot	Bland-Altman plot
LoA	Limits of agreement
ISUOG	International Society of Ultrasound in Obs&Gyn
BW	Birth weight
PPV	Positive predictive value
NPV	Negative predictive value
SFH	Symphysis-fundal height
UtA	Uterine artery
MoM	Multiple of median
EDD	Estimated due date
CAPO	Composite adverse perinatal outcome
PAPP-A	Pregnancy associated plasma protein-A
OR	Odds ratio
aOR	adjusted Odds ratio
AUC	Area under the curve
NICU	Neonatal intensive care unit
CS	Caesarean section
FMU	Fetal medicine unit
NNU	Neonatal unit
BMI	Body mass index
LSCS	Lower segment caesarean section
NCAO	Neonatal composite adverse outcome
RCT	Randomized controlled trial

ACOG	American College Obstetrics and Gynaecology
RCOG	Royal College Obstetrics and Gynaecology
ART	Assisted reproduction techniques
PE	Pre-eclampsia
DM	Diabetes mellitus
GDM	Gestational diabetes
UK	United Kingdom

Project overview

Background/ conceptual

Cohort INTERGROWTH-21st Project

Standardisation and quality control in fetal ultrasound to ensure high levels of reproducibility and accuracy of measurements

Cohort OxGRIP Project

Definition and detection of SGA, LGA and AGA in a low risk population

Clinical development

Multicentre PhD Project (Oxford / Zaragoza)

Prediction of perinatal morbidity and mortality in three high risk cohorts

SGA cohort

- Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol. Ultrasound Obstet Gynecol. 2018 Jul; 52(1):66-71
- Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term SGA fetuses. Ultrasound Obstet Gynecol. 2018 Oct; 52(4):494-500
- Clinical phenotypes for risk stratification in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2022 Apr; 59(4):490-496

LGA cohort

Ultrasound predictors of adverse outcome in pregnancy complicated by pre-existing and gestational diabetes. Acta Obstet Gynecol Scand. 2022 Jul; 101(7):787-793

AGA cohort

Abnormal umbilical artery pulsatility index in appropriately grown fetuses in the early third trimester: an observational cohort study. J Matern Fetal Neonatal Med. 2022 Dec 8;1-8

Background

Standardisation and quality control

Ultrasonography plays a crucial role in contemporary obstetric practice, especially in the identification of abnormal fetal growth patterns. Its effectiveness in recognising abnormal fetal growth depends on accurate pregnancy dating, serial growth assessment, standardisation and quality control of fetal ultrasound measurements.

Pregnancy dating

During pregnancy, accurate estimation of gestational age (GA) is essential to interpret fetal anatomy and growth patterns; predict the expected date of delivery; and determine rates of small-for-gestational-age fetuses and preterm birth accurately. Precise knowledge of gestational age is crucial to guide appropriate management and decision making in pregnancy.

Gestational age (GA) has traditionally been calculated from the first day of the last menstrual period (LMP). However, in up to 50% pregnancies the LMP is unknown or the information is unreliable due to irregular menstrual cycles [1,2]. Studies have shown that even when the LMP is sure, there is a wide distribution over GA estimates when compared with ultrasound [3]. This, in turn, may underestimate the rate of preterm delivery [4] and overestimate, the number of postdate pregnancies. Gardosi et al reported that 72% of inductions performed for post-term pregnancy according to menstrual dates were, in fact, not post-term according to ultrasound dating [5].

GA can be estimated by ultrasound measurement of fetal crown–rump length (CRL) or head circumference at < 14 weeks' and ≥ 14 weeks' gestation, respectively [6]. Between 9 and 13 weeks' gestation, the CRL shows linear increment and a rather small standard deviation, which means that GA can be estimated accurately. As the fetus enters the second and especially the third trimesters of pregnancy, constitutional and pathologic factors (aneuploidy, placental insufficiency, or overgrowth syndromes) begin to influence the fetal growth trajectory [7]. Therefore, the accuracy of ultrasound for gestational dating is highest in early pregnancy and diminishes with advancing GA.

In later pregnancy, head circumference (HC) is typically used for dating, as CRL can no longer be measured owing to curling of the growing fetus; however, variation is greater, which results in less accurate estimation of GA [8]. For this reason, first-trimester ultrasound estimation of GA is recommended in clinical practice [6].

Other fetal anatomic structures, such as the trans cerebellar diameter (TCD) demonstrate consistent growth throughout the latter half of gestation, and measurements are reliably correlate with GA. TCD maintain its relationship with GA even when growth abnormalities are present, making this measurement particularly useful in those pregnancies in which growth abnormalities are suspected but the gestational dates are non-verified. The TCD is easily measured in the axial oblique posterior fossa view and, in euploid fetuses with a structurally normal cerebellum, it has a linear correlation with GA. It is important to note that the GA-TCD correlation appears to be largely preserved in the settings of FGR and macrosomia [9,10].

CRL measurement

Measurement of fetal crown–rump length (CRL) is the method of choice for ultrasound assessment of gestational age in the first trimester [11], but it is susceptible to intra-observer and inter-observer variation. This is mainly secondary to inconsistent or incorrect acquisition of the appropriate images. For example, a parasagittal plane may not contain the entire fetal length, leading to CRL underestimation; conversely, a hyper-extended fetal neck will lead to CRL overestimation [12].

Standardisation and quality control of CRL measurements are essential to ensure high levels of reproducibility and accuracy of pregnancy dating. Standardised criteria [12] for a correct generation of a CRL imaging plane and calliper application (figure 1) are:

- Good magnification with the fetus filling almost the entire screen

- Mid-sagittal section with fetal profile, spine and rump completely visible

- Neutral position with fluid visible between the chin and the chest of the fetus

- Fetus in horizontal position (90 degree to the ultrasound beam)

- Crown and rump clearly visible

- Callipers correctly placed with the intersection of the callipers on the outer borders of the skin over the head and rump.

Figure 1 – Measuring the crown rump length (CRL)

Fetal biometry

Biometric measurements to assess fetal growth are: head circumference (HC), abdominal circumference (AC), and femur length (FL). These biometric measurements can be combined into an estimated fetal weight (EFW) using various formulae, in order to provide a more straightforward and clinically relevant estimate of fetal growth.

The description of the EFW is usually grouped into 3 different categories. A fetus, whose estimated weight for a given gestation, is between the 10th and 90th percentiles, is described as appropriate for gestational age (AGA). Small for gestational age (SGA), refers to a fetus that has an EFW below the 10th percentile. The term large for gestational age (LGA), refers to a fetus with an EFW above the 90th percentile.

Fetal size can be assessed at a specific time point or dynamically over time. These two approaches serve distinct purposes in monitoring and evaluating fetal growth during pregnancy. While the assessment of biometric measurements at a specific time point provides a snapshot of the fetus's size and development at a particular moment, the assessment of fetal growth trajectory looks at the dynamic growth of the fetus over time. It requires multiple measurements taken at different points during the pregnancy to create a growth curve or trajectory.

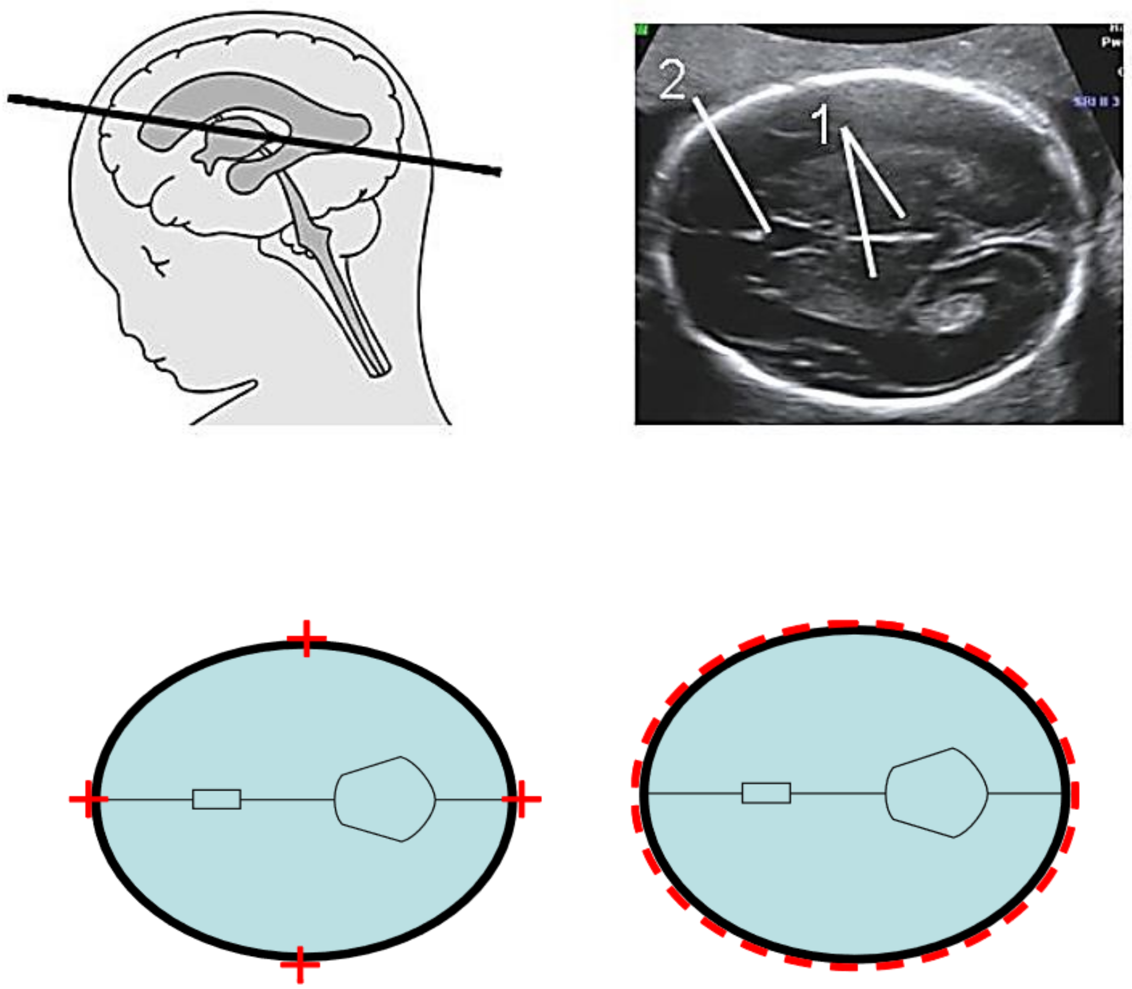
Deviations from the expected growth trajectory can indicate potential issues that may require further investigation or intervention.

Standardization and quality control (QC) of fetal ultrasound biometry are essential to ensure high levels of reproducibility and measurement accuracy is critical for detecting abnormal fetal growth. In fact, avoiding false-positive findings, which are associated with attendant anxiety and risk of unnecessary interventions, is almost as important in antenatal care as are diagnostic failures.

For a QC system in fetal biometry to be useful clinically, multiple strategies need to be employed [13], such as (1) qualitative scoring of ultrasound images against predefined criteria [14] and (2) quantitative assessment of measurements and comparison with their expected distributions [15].

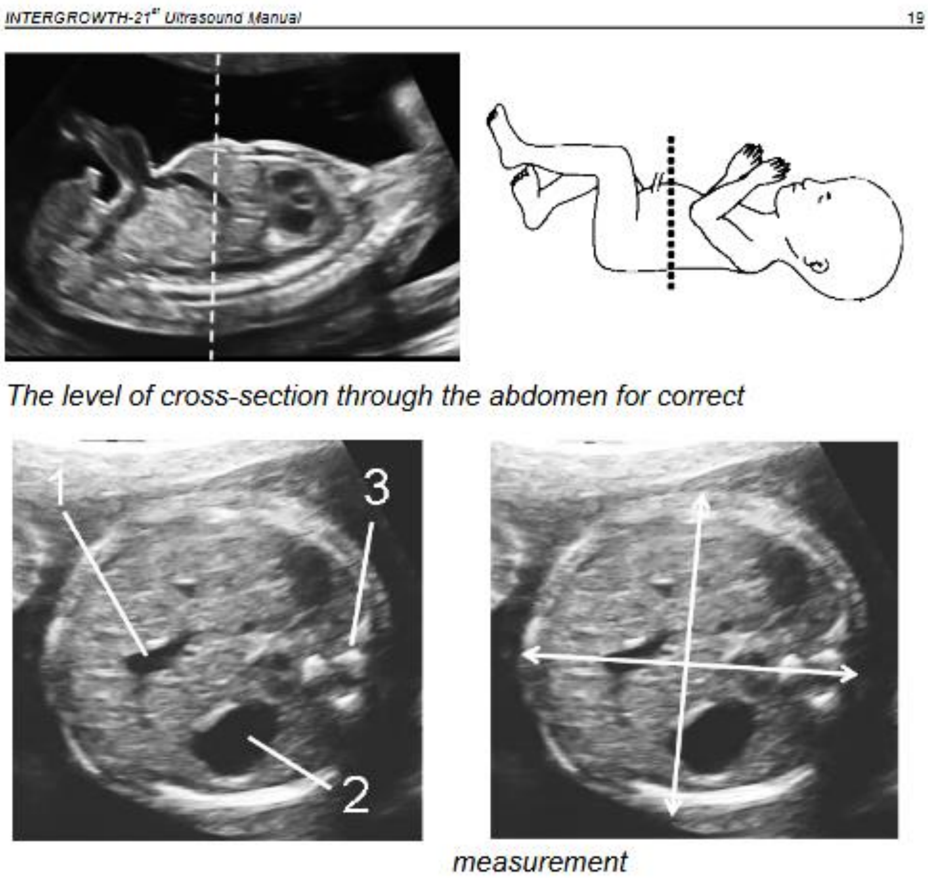
The goal of standardisation is to ensure that all sonographers take measurements in an identical fashion. Head measurements (figure 2) should be obtained in the transthalamic plane, placing the calipers on the outer border of the skull, using both the ellipse facility and two perpendicular diameters.

Figure 2 – Obtaining head measurements: biparietal diameter (BPD), occipito-frontal diameter (OFD), head circumference (HC) using ellipse facility



Abdominal measurements (figure 3) should be obtained in an axial plane, with the umbilical vein in the anterior third of the fetal abdomen (at the level of the portal sinus) and the stomach bubble visible. Again, both the ellipse facility and the two-diameter method were used, placing the calipers on the outer border of the body outline (skin covering).

Figure 3 – Obtaining abdominal measurements: antero-posterior abdominal diameter (APAD), transverse abdominal diameter (TAD), abdominal circumference (AC) using ellipse facility



CORRECT:

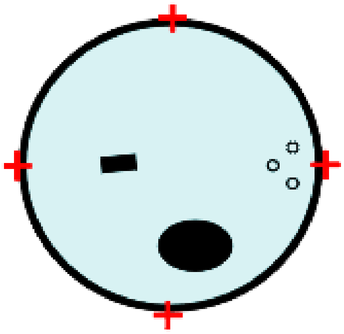
-The image is well magnified

-The section is circular.

-The landmarks are seen:

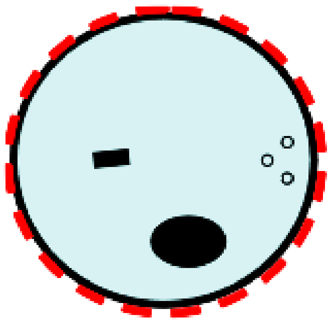
1. *Short segment of umbilical vein in the anterior third.*
2. *Stomach bubble visible.*
3. *Spine.*

- The bladder and kidneys are not visible



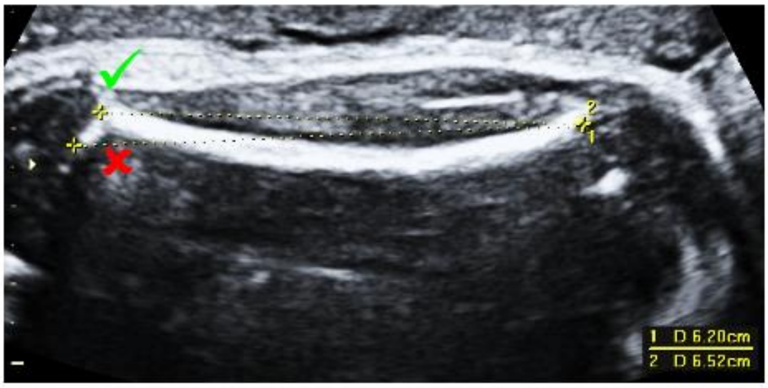
The callipers are positioned correctly, outer to outer.

When using the ellipse facility this should run along the outer border of the abdomen.

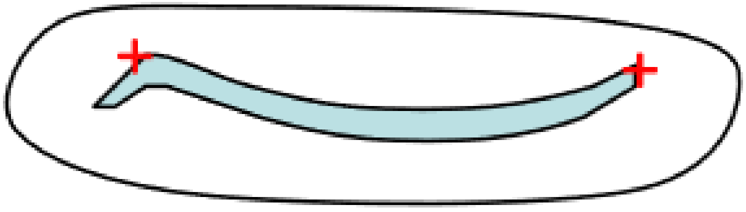


For FL (figure 4), the femur closest to the probe should be measured with its long axis as horizontal as possible. Calipers were placed on the outer borders of the diaphysis of the femoral bone (‘outer to outer’) [16].

Figure 4 – Obtaining femur length measurement



The greater trochanter should be avoided in measuring the femur length as this results in an excessive measurement (red X)



INTERGROWTH-21st Ultrasound Operations Manual

Qualitative scoring of ultrasound images has been described by Cavallaro et al [16]. Images are scored based on a set of criteria, each worth 1 point towards the total score, with a maximum of 6 points for HC and AC, and 4 points for FL (table 1).

Table 1 - Image scoring criteria used for standardization and quality control of ultrasound for fetal biometric measurement of headcircumference (HC), abdominal circumference (AC) and femur length (FL) [16]

*Cephalic plane (HC)**	*Abdominal plane (AC)**	*Femoral plane (FL)†*
Symmetrical plane	Symmetrical plane	Both ends of bone visible clearly
Thalami visible	Stomach bubble visible	Angle < 45°
Cavum septi pellucidi visible	Portal sinus visible	Femur occupying at least 30% of image
Cerebellum not visible	Kidneys not visible	Calipers placed correctly
Head occupying at least 30% of image	Abdomen occupying at least 30% of image	—
Calipers/ellipse placed correctly	Calipers/ellipse placed correctly	—

*Maximum of 6 points. †Maximum of 4 points.

All images are self-scored at the time of scanning by the sonographer taking the image. A randomly chosen sample of 10% of all these images are re-scored by a reviewer.

Comparison between self- and reviewer scoring is undertaken using an adjusted kappa statistic (interobserver variability of image scoring). A kappa value of more than 0.6 is considered a priori as an acceptable level of agreement among sonographers.

Quantitative quality control with assessment of intra- and interobserver variation in biometric measurements has been also described by Cavallaro et al [16]. For each fetal biometric variable (HC, AC, FL), the variability of the measurements is assessed using Bland–Altman plots [17].

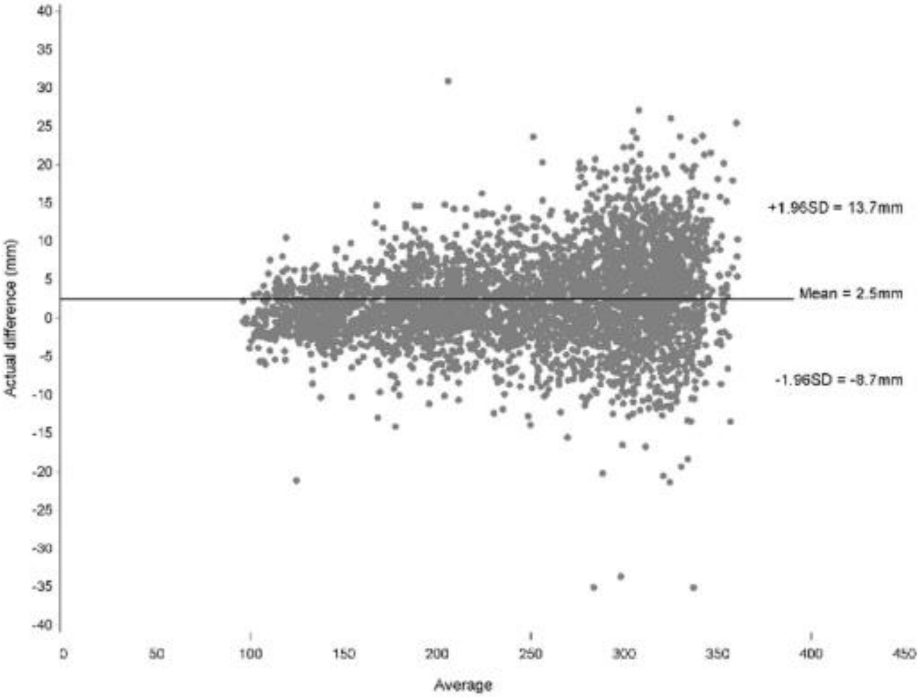
The Bland–Altman plot is a method for comparing two measurements of the same variable [17]. The concept is that Y-axis is the difference between the two measurements. An ideal measurement tool should obtain exactly the same results when measurements are obtained with one method or another. So, all the differences would be equal to zero [17].

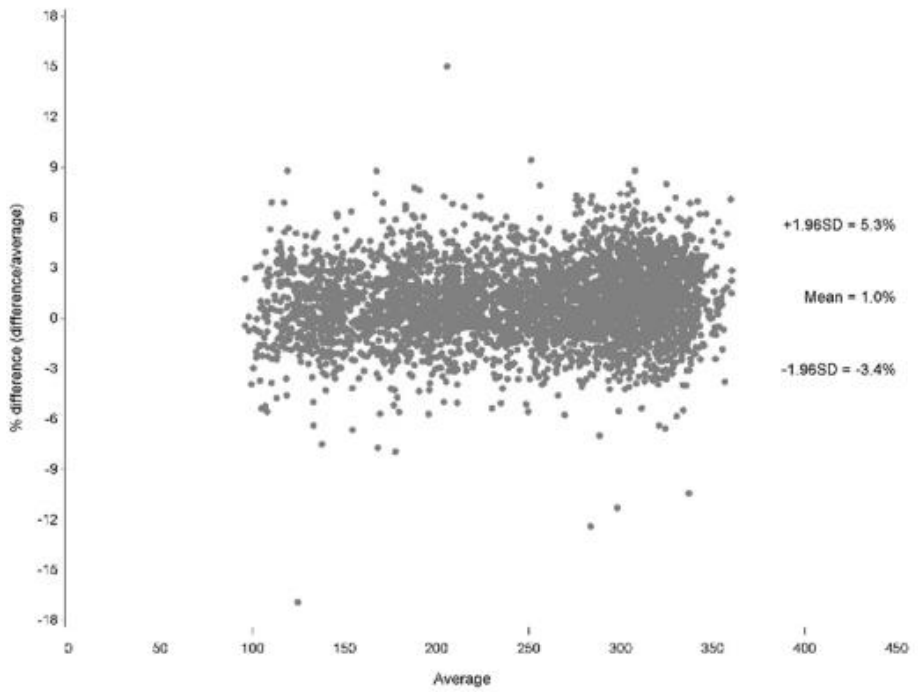
If neither of the two methods is a "reference", the differences could be compared with the mean of the two paired values, which is the value reported on the X-axis. The Bland–Altman graph plot simply represents every difference between two paired methods against the average of the measurement. Plotting difference against mean allows to investigate any possible relationship between measurement error and the true value. But since we do not know the true value, the mean of the two measurements is the best estimate we have [18].

The Bland–Altman plot (figure 5) can therefore highlight anomalies, for example, if one method always gives too high a result, then all points are above or below the zero line. It can also reveal that one method overestimates or underestimates values at a specific cut off of the mean of two measurements (X-axis) [18].

Instead of simply expressing differences within observers as actual measurement units (mm), Cavallaro et al [16] has also described a pairwise comparisons using percentage to account for changes in fetal size with increasing gestational age. The difference between two selected measurements is calculated and expressed as a percentage of their mean, then plotted against this mean. The 95% limits of agreement (LoA) are calculated and marked on the plots, giving a quantifiable estimate for measurement variability associated with acquiring an image and positioning the callipers.

Figure 5 - Bland–Altman plots showing inter-observer variability with measurements expressed in mm and as percentage (%) [16]





This type of quality control monitoring allows consistency and high reproducibility in fetal biometry, minimising systematic errors and avoiding false-positive or false-negative findings in clinical practice.

Doppler measurements

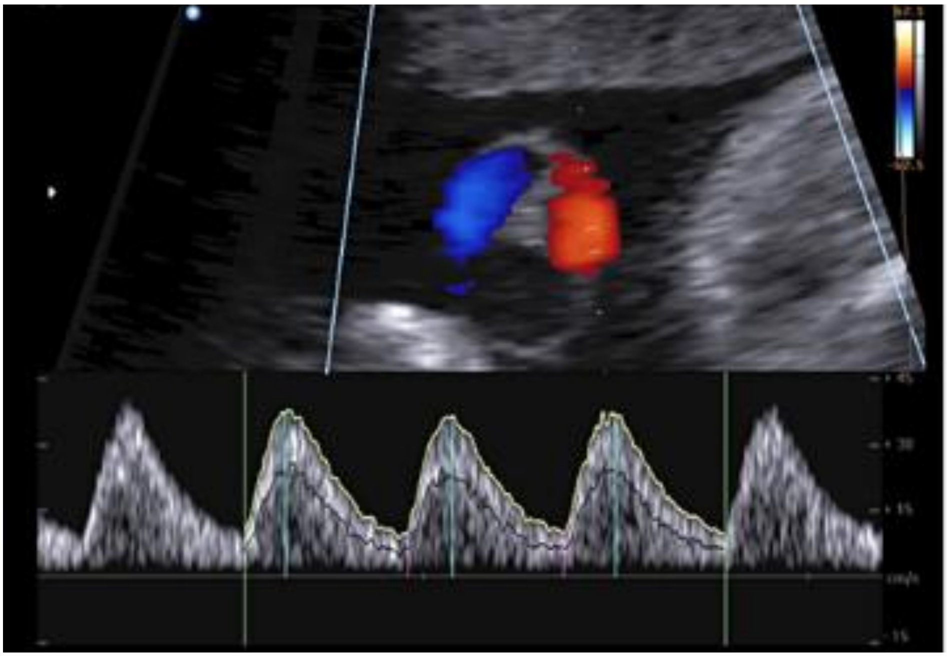
Doppler ultrasonography is a non-invasive method of evaluating blood flow in vivo, and plays an important role in identifying and managing high risk pregnancies [19]. In high-risk women, especially those with hypertensive disease and suspected FGR, the use of Doppler ultrasound is associated with reduced incidence of perinatal deaths and unnecessary medical interventions [20].

However, poor technique may result in normal blood flow to appear suboptimal; for example, a poor angle of insonation may make end-diastolic flow disappear in umbilical artery Doppler waveforms, creating false positives. Conversely, when assessing uterine artery flow, false negatives may arise from insonating low-resistance spiral vessels, instead of uterine arteries.

The International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) practice guidelines for use of Doppler in pregnancy recommend considering a number of factors to optimize image quality and improve the accuracy and reproducibility of measurements [21]. These include: obtaining the recordings during fetal quiescence in the absence of breathing or body movements; considering use of colour flow mapping to identify the vessels of interest; and ensuring optimal angle of insonation, horizontal sweep speed, and gain and pulsed-wave frequency [21].

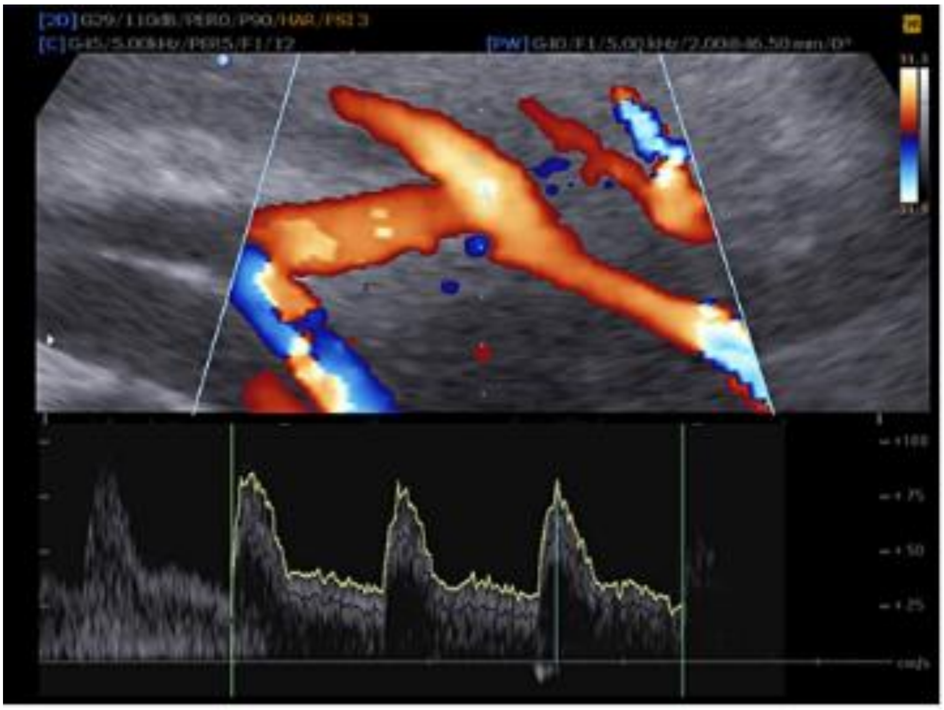
Molloholli et al [22] developed an objective image-scoring system for Doppler ultrasound of the fetal umbilical and maternal uterine arteries. For umbilical artery Doppler (figure 6), authors suggested that the signal was obtained from a free loop of the umbilical cord during a period of fetal quiescence (absence of significant limb or breathing movements); having identified the vessel with colour Doppler, four to six consistent waveforms were obtained with the pulsed-wave Doppler gate.

Figure 6 – Obtaining umbilical artery Doppler



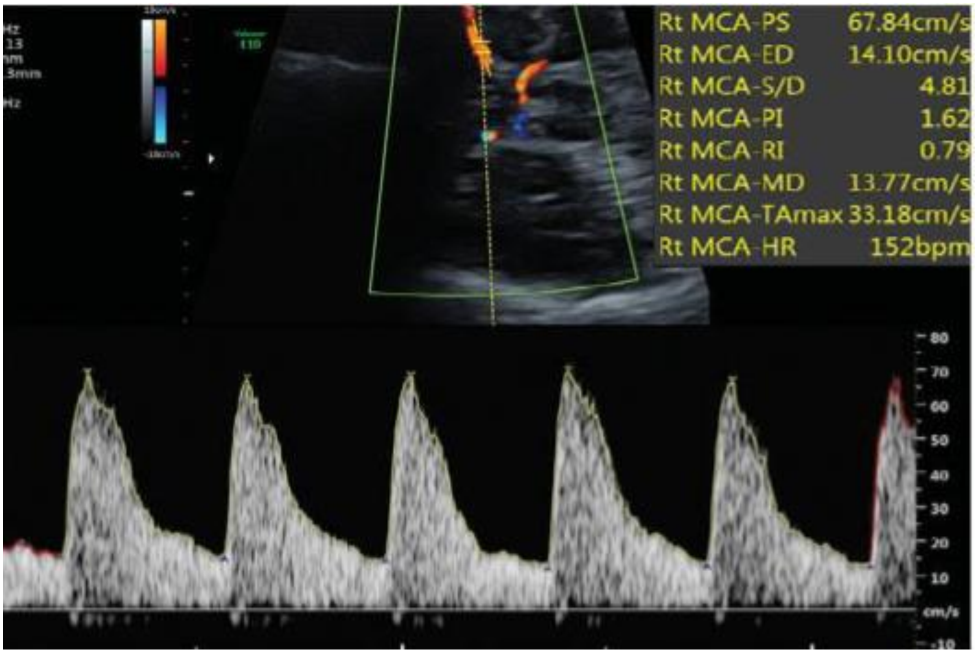
For uterine artery Doppler assessment (figure 7), each artery was identified using colour flow mapping at the crossover with the external iliac artery; four to six similar waveforms were then obtained with pulsed-wave Doppler using an appropriate gate size and minimum angle of insonation.

Figure 7 – Obtaining uterine artery Doppler



Ruiz Martinez et al [23] developed an objective image-scoring system for Doppler ultrasound assessment of the middle cerebral artery (MCA). An axial plane of the fetal brain with visualisation of the thalami and sphenoid wings, and identification of the circle of Willis using colour Doppler should be obtained. The pulsed-wave Doppler gate should be placed at proximal third of MCA (figure 8).

Figure 8 – Obtaining middle cerebral artery Doppler



For objective assessment, a similar six-point image-scoring system was developed by both research groups, based on recommended and established standards for Doppler measurements:

- Magnification: area of interest fills 50% of screen
- Angle of insonation between vessel tract and Doppler beam < 15 ° for MCA and < 30 ° for umbilical artery and uterine artery.

- Sweep speed: four to six waveforms with consistent and similar signal
- Image clarity: clear waveform, without artefacts, and accurate trace (avoid venous signal, especially for umbilical artery)
- Anatomical site of sample:
  - Umbilical artery: insonation of free loop of cord
  - Uterine artery: insolation before bifurcation above iliac vessels
  - Middle cerebral artery: identification of circle of Willis, and pulsed-wave Doppler gate placed at proximal third of MCA
- Velocity scale: 75% of peak systolic velocity

For each criterion, reviewers assigned a score of 1 or 0 depending on whether the criterion was met or not, respectively. The authors [22,23] demonstrated that this six-point scoring system was more reproducible ensuring accurate Doppler assessment.

Defining abnormal fetal growth

An estimated fetal weight (EFW) below the 10th centile is generally considered predictive of adverse perinatal outcome, but not all fetal growth restricted fetuses have EFW below the 10th centile and many are merely constitutionally small [24]. Despite this limitation, detection rates of SGA (EFW < 10th centile) remain a frequently used performance indicator in several countries, including the UK.

Large-for-gestational age (LGA) is usually defined as birth weight (BW) above the 90th centile and has been shown to be associated with adverse outcome, including emergency caesarean section, postpartum haemorrhage, perineal trauma, shoulder dystocia, brachial plexus injury and fractures [25]. Thus, the detection of LGA has important medicolegal implications for patient counselling and delivery planning.

The choice of EFW and BW reference charts is important, and arguments supporting the use of any one chart over others often concentrate on the methodological strength of the sample analysis or its suitability for the specific population it is meant to describe [26].

Controversy surrounds the choice of EFW and BW charts and, in particular, the distinction between prescriptive, descriptive and customized charts. Prescriptive charts, like the INTERGROWTH-21st and WHO (World Health

Organization) charts, are designed to benchmark expected fetal growth under ideal or optimal maternal health conditions. These charts are based on data from diverse populations around the world and aim to establish a standard for fetal growth that is not influenced by factors such as maternal height, weight, or ethnicity. The goal is to provide a universal reference for assessing fetal growth and development.

Descriptive charts, such as the Hadlock chart, describe the range of observed fetal growth within a specific population over a particular time period. These charts are based on data collected from a particular group of pregnant individuals, which may not necessarily represent an ideal or optimal standard. Descriptive charts provide information on how fetal growth varies within a specific population but may not be applicable for assessing growth in populations with different characteristics or health conditions.

Customized charts take into account maternal characteristics, such as height, weight, parity (number of previous pregnancies), and ethnicity, in addition to fetal measurements. These charts aim to provide a more personalized assessment of fetal growth by considering the individual characteristics of the mother. This approach can help account for variations in fetal growth that may be influenced by maternal factors [27-29]. The scientific debate as to which reference chart (either prenatal or postnatal) is the best is endless and may never be resolved. However, the main issue is that the combination of EFW and BW charts has the potential to create wide variation in the detection of SGA and LGA in the same population.

Mathewlynn et al [30] demonstrated that different combinations of EFW and BW charts can yield vastly different detection rates (sensitivity) in the same population cohort and time period. The sensitivity of EFW < 10th centile for the detection of BW < 10th centile ranged from 10.8% to 66.8% and the sensitivity of EFW < 3rd centile for the detection of BW < 3rd centile ranged from 4.1% to 66.8%, depending on the charts used. The sensitivity of EFW > 90th centile for BW > 90th centile ranged between 22.9% and 68.3%.

Using an ultrasound chart that yields a very low incidence of EFW-SGA or -LGA (screen-positive rate) and then a BW chart that yields a much larger incidence of BW-SGA or –LGA (outcome rate) in the same population leads to an inevitable poor detection rate. Conversely, combining an EFW chart that overestimates the number of SGA or LGA cases with a BW chart that underestimates the same, it can lead to an overinflated LGA detection rate with poor specificity and high number of false positives. In the context of fetal growth assessment, this can result in unnecessary medical interventions. Mathewlynn et al [30] concluded that unless there is consistency in the use of estimated-fetal weight and birth weight reference charts, comparison of detection rates between care providers may be misleading.

Despite its pitfalls in centile estimation, EFW remains a clinically important part of ultrasound assessment of fetal wellbeing. However, although an EFW below the 10th centile is associated with an increased risk of adverse outcomes, in reality many of these SGA infants are physiologically small and about 80% of adverse perinatal events occur in the group with a weight ≥ 10th centile. Therefore, categorization of the at-risk fetus according to size alone is inadequate and EFW should be used as part of a multifactorial algorithm for the prediction of neonatal adverse outcomes.

Detection of abnormal fetal growth

Late pregnancy ultrasonography, also known as third trimester ultrasound, plays a crucial role in monitoring the well-being of both the fetus and the mother. The practice of selectively scanning women in late pregnancy based on risk factors, obstetric complications, and serial measurements of symphysis-fundal height (SFH) is common in many countries. However, the introduction of universal late pregnancy ultrasonography has been suggested to enhance the detection of abnormally growing fetuses, especially those classified as small for gestational age (SGA).

A Cochrane meta-analysis of nine trials, assessing universal late pregnancy ultrasonography as screening tool for neonatal adverse outcomes and including about 27.000 women, showed no beneficial effect, which led to a recommendation against offering such screening routinely in the third trimester.

However this meta-analysis had some important pitfalls. Screening is a two-stage process. First, a screening tool should identify those at risk of developing disease. Second, an intervention should be available to reduce the risk of disease development in those at high risk. It follows, therefore, that a successful screening programme must address both elements of the process [31].

Ultrasonography is a valuable screening tool in obstetrics for assessing fetal well-being and predicting adverse outcomes, but the quality and reliability of the results depend on several key factors:

- *Reference ranges for fetal biometry:* accurate interpretation of fetal measurements, such as head circumference, abdominal circumference, and femur length, relies on established reference ranges for each gestational age. Using incorrect or outdated reference ranges can lead to misinterpretations.
- *Timing of the scan:* the gestational age at which the scan is performed is crucial. Different features and measurements are most accurate and relevant at different stages of pregnancy. For example, the first-trimester scan is crucial for dating the pregnancy, while the third-trimester scan may focus on growth and fetal well-being.
- *Technique and equipment:* the choice of ultrasound equipment, settings, and transducers can affect the quality of the images and measurements. It's essential to use appropriate techniques to ensure accurate results.
- *Assessment of Doppler flow velocimetry:* Doppler ultrasound can assess blood flow in maternal, placental, and fetal blood vessels. It is used to evaluate placental function and fetal well-being. Standardized protocols

and interpretation criteria are essential to ensure consistency and accuracy.

- *Standardization and quality control:* adherence to established protocols, regular training and quality control measures for ultrasound operators can minimize errors and ensure the consistency and accuracy.

Hence, combining data from studies with variations in scan protocols, equipment, measurements, and definitions of "screen positive" can introduce significant bias and limit the reliability of results.

Furthermore, comparing study cohorts with different a priori risk for adverse outcomes is problematic. Studies included in the Cochrane meta-analysis were not confined to first pregnancies. In women without risk factors who had a previous uncomplicated birth, the a priori risk of severe adverse events would be so low that even a very effective screening test would have a low positive predictive value (PPV). Conversely, some studies included women with previous complicated pregnancies and high-risk women for which a significant risk of adverse outcomes would persist even if the test produces a negative result due to high prevalence of complications (low negative predictive value).

As previously mentioned, a clinically effective programme of screening and intervention also requires that the screening test is coupled to an intervention that reduces the risk of the given outcome in high-risk pregnancies. The main intervention in the third trimester of pregnancy is the decision to effect a medically indicated delivery. Routine early-term delivery (at 37–38 weeks of gestation) reduces perinatal mortality but infant mortality and childhood neurodevelopmental complications are higher than after birth at 39-41 weeks [32-35]. Screening low-risk or unselected pregnant women in the early third trimester can potentially cause high number of false positives, and consequently more interventions. Expedited birth may therefore cause considerable but unmeasured harm in many, for the benefit of few [31].

None of the studies listed in the Cochrane review coupled the screening test to an intervention, therefore it is difficult to know the effect of the screening programme on stillbirth rate, perinatal mortality and other neonatal adverse outcomes. In addition, the Cochrane meta-analysis only included 15% of the sample size required for adequate statistical power to study perinatal death. Therefore, correct conclusion of the meta-analysis is that it is not known whether late-pregnancy ultrasound in low-risk or unselected populations confers benefit on mother or baby.

Several studies [36-38] demonstrated that while universal third-trimester ultrasound may not be very sensitive in detecting SGA or LGA fetuses in a low-risk population due to a significant number of false negative results, its accuracy improves when it's performed closer to delivery. On the other hand, ultrasonography is quite specific for both SGA and LGA meaning that a fetus who has an estimated fetal weight between the 10th and the 90th centile is likely to have a birth weight which follows in this same range. Again specificity improves when ultrasound assessment is performed closer to delivery. Overall ultrasound is a more reliable tool than SFH measurement for assessing fetal size and predicting birth weight.

Detection of FGR neonates

Ciobanu et al [36] demonstrated that the predictive performance in identifying SGA neonates is higher when the ultrasound scan is carried out at 35^{+0} to 36^{+6} weeks' gestation compared to scans performed at 31^{+0} to 33^{+6} weeks. Using estimated fetal weight (EFW) as a screening method provides better predictive performance compared to measuring fetal abdominal circumference (AC). Using a more stringent threshold, such as birth weight below the 3rd percentile, yields better predictive performance compared to using the 10th percentile as the threshold. The predictive performance is higher when considering delivery within 2 weeks after assessment rather than at any stage after assessment.

Screening by EFW < 10th centile at 35 + 0 to 36 + 6 weeks' gestation predicted 70% and 84% of neonates with birth weight < 10th and < 3rd percentiles, respectively, born within 2 weeks after assessment, and the respective values for a neonate born at any stage after assessment were 46% and 65%. Prediction of > 85% of SGA neonates with birth weight < 10th percentile born at any stage after screening at 35 + 0 to 36 + 6 weeks' gestation requires use of EFW < 40th percentile. Screening at this percentile cut-off predicted 95% and 99% of neonates with birth weight < 10th and < 3rd percentiles, respectively, born within 2 weeks after assessment, and the respective values for neonates born at any stage after assessment were 87% and 94%. However, this also increased the number of false positives. Only about one in 4 of such fetuses would actually be SGA at birth [36]. Therefore, they suggested that other parameters to assess fetal wellbeing are needed to distinguish between true and false positive in order to avoid unnecessary interventions.

Sovio et al [39] demonstrated that a policy of universal ultrasonographic estimation of fetal weight at 28 and 36 weeks' gestational age had a higher sensitivity (57%) compared to selective ultrasonography (20%) in detecting birth weight < 10th centile. However, selective ultrasonography had a higher specificity (98%) compared to universal ultrasonography (90%). This means that selective ultrasonography had a lower rate of false positives, which is important for avoiding unnecessary interventions or concerns for mothers. After the absolute numbers of true and false positives were calculated, their findings showed that for every additional SGA infant correctly identified by universal ultrasonography, about two additional results were false positives.

On the basis of these results, it appears clear that the decision to implement such screening should consider the balance between benefits and potential harm, as well as the ability to differentiate between healthy constitutionally small infants and those with growth issues. The authors suggested that assessment of abdominal circumference (AC) growth velocity might be a more appropriate marker to identify a subset of FGR which may benefit from early intervention.

Akolekar et al [37] demonstrated that despite the increased risk for low birth weight neonates, 84% of adverse perinatal outcomes, defined as stillbirth, neonatal death or neonatal unit admission for ≥48 h, occurred in the group with birth weight above the 10^{th} percentile. This means that a significant number of adverse outcomes happens in neonates with birth weights considered to be within the normal range (above the 10^{th} percentile).

The group with EFW < 10^{th} percentile contained 83%, 65% and 40% of SGA neonates with birth weight < 3^{rd} percentile delivered at ≤ 2, 2.1–4 and > 4 weeks after assessment, respectively. The respective values for a SGA neonate with birth weight < 10^{th} percentile were 69%, 45% and 30% and those for adverse perinatal outcome were 26%, 9% and 5%.

These results clearly demonstrate that timing of delivery after assessing EFW is crucial. The prediction of a SGA neonate and adverse outcome was moderate for those delivered at ≤ 2 weeks after assessment but poor for those delivered at > 2 weeks after assessment.

For this reason, the authors proposed a risk stratified approach to pregnancies undergoing routine ultrasound assessment between 35 $^{+0}$ and 36 $^{+6}$ weeks' gestation into four management groups based on findings of EFW and Doppler indices [37]:

- *High-risk:* EFW < 10th percentile or EFW ≥ 10th and < 40th percentile with highly abnormal Doppler i.e. at least one of UtA-PI MoM > 95th percentile, UA-PI MoM > 95th percentile or MCA-PI MoM < 5th percentile.
- *Intermediate-risk:* EFW between the 10th and 20th percentiles or EFW ≥ 10th and < 40th percentile with moderately abnormal Doppler i.e. at least one of UtA-PI MoM between the 90th and 95th percentiles, UA-PI MoM between the 90th and 95th percentiles or MCA-PI MoM between the 5th and 10th percentiles.
- *Low-risk:* EFW between the 20th and 40th percentiles and normal Doppler.
- *Very low-risk:* EFW ≥ 40th percentile, irrespective of Doppler findings.

The high-risk group required continuous monitoring from the initial assessment up to the delivery. The intermediate-risk group required monitoring starting two weeks after the initial assessment, continuing until delivery.

In the low-risk group, monitoring began four weeks after the initial assessment and continued until delivery. The very low-risk group did not require any further reassessment [37].

This proposed new approach for stratifying pregnancies into management groups based on findings of EFW and Doppler indices improved screening performance, especially for neonates delivered at > 2weeks after assessment (prediction of BW < 3rd centile for deliveries at ≤ 2, 2.1–4 and > 4 weeks after assessment was 89% and 75%, 83%; prediction of BW < 10th centile was 74%, and 88% and 82%, respectively).

The predictive performance for adverse perinatal outcome of EFW < 10th percentile was very poor (26%, 9% and 5% for deliveries at ≤ 2, 2.1–4 and >4 weeks after assessment, respectively) and this was improved by the proposed new approach (31%, 22% and 29%, respectively).

These evidences suggest that increasing the detection rate of birth weight < 10th centile does not significantly improve the prediction of perinatal adverse outcomes not least because many SGA babies are not growth restricted [40,41] and birth weight < 10th centile comprise less than a quarter of stillbirths [42]. Nevertheless, impaired placental function may be present in about half of stillbirths [43]. About 50-60% of SGA fetuses are physiologically small and therefore they are at low risk for adverse perinatal outcome. In contrast, FGR fetuses are pathologically small, irrespective of the growth centile (which can be > 10th centile), and therefore at increased risk of adverse perinatal outcome.

Using the EFW < 10th centile alone to define fetuses "at risk" inevitably causes over diagnosis of constitutionally small fetuses (false positive) for which expedite birth is more likely to be harmful rather than beneficial; and under diagnosis of FGR fetuses with an EFW > 10th centile (false negative) for which intervention instead is likely to improve outcomes.

In order to better identify fetuses at risk and to better compare true FGR cohorts with appropriately grown cohorts, a Delphi consensus (table 2) [44] defined the criteria to distinguish FGR from SGA. These include sequential ultrasound measurements focusing on declining/crossing growth centiles and functional parameters such as Doppler waveform analysis (umbilical artery (UA), fetal middle cerebral artery, and uterine arteries).

Table 2 - Definitions for early and late fetal growth restriction (FGR) in absence of congenital anomalies according to Delphi consensus [44]

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3rd centile *or* UA-AEDF	AC/EFW < 3rd centile
Or 1. AC/EFW < 10th centile *combined with* 2. UtA-PI > 95th centile *and/or* 3. UA-PI > 95th centile	*Or at least two out of three of the following* 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles >2 quartiles on growth centiles* 3. CPR < 5th centile *or* UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

Universal third-trimester scan and FGR detection in Oxford

In 2016 a universal 36-week ultrasound scan was introduced for all pregnant women at the Oxford University Hospitals NHS Foundation Trust (OUH): the Oxford Growth Restriction Identification Programme (OxGRIP). This study [45] aimed to investigate the impact of the OxGRIP initiative in the population of women who gave birth in Oxfordshire in the study period on perinatal morbidity and mortality.

Before OxGRIP implementation, women with an EDD before 01/Oct/2016 had ultrasound scans in the third trimester only if clinically indicated, on the basis of risk factors or new pregnancy complications24. The EFW and UmbA-PI were recorded. Suspected SGA fetuses with EFW < 10th centile or umbA-PI > 95th centile were referred to a dedicated and consultant led SGA clinic.

Following OxGRIP implementation, all women with an EDD from 01/Oct/2016 were offered a universal ultrasound between 35+0 and 36+6 weeks. The EFW, UA-PI, MCA-PI, CPR and AC growth velocity were recorded. Women were considered 'screen positive' and referred for secondary assessment and intervention in a specialist consultant-led SGA clinic not only when EFW < 10th centile [46], or when UA PI > 95th centile, but also if the CPR <1.1, or if there was a > 40 centile point AC growth deceleration compared to the 20-week scan.

At the consultant-led SGA clinic appointment, all fetal measurements and Doppler investigations were repeated including umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI, cerebroplacental ratio (CPR), uterine artery PI and calculation of low abdominal circumference (AC) growth velocity, defined as a >40-centile reduction from the 20-week scan. Expectant management or expedited birth was offered according to a modification of a published protocol (figure 9) [47] depending on the presence of abnormal growth and Doppler parameters or other maternal risk factors.

Treatment paradox prevented calculation of screening performance of the referral criteria for mortality, but the detection rate of birth weight < 10th centile [48] pre- and post-OxGRIP was investigated.

Outcomes for the period before and after OxGRIP implementation were compared. A priori primary outcome measures were: 1) extended perinatal mortality - stillbirths and neonatal deaths up to 28 days per 1000 total births; 2) composite adverse perinatal outcome-1 (CAPO-1) defined as extended perinatal mortality or Sarnat's [49] encephalopathy grade II or III : a surrogate for 'mortality or severe morbidity'; and 3) expedited birth, defined as induction of labour or pre-labour caesarean section. Several a priori secondary outcomes of perinatal mortality and morbidity were used, including two composite adverse perinatal outcomes replicated from recent studies CAPO-2 [39] and CAPO-3 [50].

Figure 9 - Management protocol of SGA fetuses

Referral criteria following 36-week growth scan

1) EFW <10^{th} centile
2) AC reduction > 40 percentile points
3) Isolated CPR < 1.1 or isolated Umbilical PI >95^{th} centile

Check:

1) EFW incl ACGV (consider sex adjustment: female fetus: 10^{th} centile is total population 8^{th} centile; male fetus 10^{th} centile is total population 12^{th} centile)
2) CPR
3) Uterine arteries

Management in FGA clinic

<u>36-37 weeks:</u>

- Deliver if EFW <10^{th} centile AND CPR < 1.1 or Umbilical PI > 95^{th} centile, OR EFW <1^{st} centile
- Deliver, irrespective of EFW, CPR<1.0 OR umbilical artery AEDF
  For both categories please perform CTG in clinic

Otherwise reassess </=2 weeks (clinical judgement to determine which) and see below

<u>From 37+0 weeks:</u>

Apply same criteria as for 36 weeks and

Deliver if:

- EFW <3^{rd} centile
- EFW >3^{rd} <10^{th} centile AND CPR < 1.1 (do CTG if <1.0); Umbilical PI > 95^{th} centile, or ACGV reduction <10^{th} centile)
- EFW >3^{rd} <10^{th} centile AND 1+ of the following criteria →
- CPR < 1.1 AND 1+ of the following criteria →

Following criteria:

- Abnormal uterine arteries: 20 weeks total PI > 2.5 or current total PI > 2.0
- Maternal age >/= 40
- PAPP-A < 0.3 MoMs
- Medicated hypertension (note for preeclampsia deliver > 36 weeks anyway)
- Diabetes with poor control/ AC >95^{th} centile (note delivery plan should be in place)

All else normal: review at the following intervals:

1 week:

- Isolated CPR < 1.1

2 weeks:

- All others i.e., Isolated EFW >3^{rd} centile with no complicating features
- Isolated ACGV reduction (>40 centile points or <10^{th} centile) from the anomaly scan with (above) no complicating features

<u>From 38 weeks:</u>

Apply same criteria as for 36 and 37 weeks

<u>From 39 weeks:</u>

Apply same criteria as for 36 and 37 weeks

<u>From 40 weeks:</u>

Deliver all referral criteria, and any of age >/=40, AC reduction or PAPP-A <0.3MoMs by 41 weeks

Note: follow separate induction guideline pertaining to abnormal uterine arteries and low PAPP-A, maternal disease, and age irrespective of scan findings: some will have del indicated before suggested by this guideline.

The detection of birth weight < 10^{th} centile using EFW < 10^{th} centile increased from 25.7% to 31.4% (aOR 1.44; 95%CI 1.18-1.76); the detection of birth weight < 3^{rd} centile using EFW < 3^{rd} centile increased from 21.6% to 26.9% (aOR 1.03; 95%CI 0.61-1.72). This was because, despite the increase in the number of scans, the proportion that had an EFW<10^{th} or 3^{rd} centile dropped considerably: for the former from 10.7% to 4.1%. If, however, 'screen positive' (including other scan parameters), as opposed to EFW alone, was used as the criterion for detection of birth weight < 10^{th} centile and < 3^{rd} centile, the detection rates were 40.5% and 57.2%, respectively.

For the outcomes in the pre- and post-exposure groups (table 3), extended perinatal death reduced from 1.7/1000 births to 1.2/1000 (OR 0.72; 95%CI 0.42-1.23). CAPO-1 (extended perinatal mortality or encephalopathy Grade 2-3) reduced from 2.9/1000 to 1.9/1000 total births (OR 0.67; 95%CI 0.44-1.02). There was an increase in expedited births from 35.2% to 37.7% (OR 1.11; 95%CI 1.07–1.16).

Whilst the proportion affected by CAPO-2 (a replication of Sovio et al [39]) reduced little (9.2/1000 to 8.7/1000 total births) (aOR 0.89; 95%CI 0.71-1.12), those affected by CAPO-3 (a replication of Heinrichs et al [50]) reduced significantly (24.6/1000 to 21.4/1000 total births) (aOR: 0.81; 95%CI 0.70–0.94). No significant differences were found for other perinatal or neonatal outcomes except a marginal reduction in low Apgar scores and all grades of hypoxic-ischaemic encephalopathy.

Table 3 – Perinatal outcomes before and after universal late third trimester ultrasound [51]

Variable	pre-OxGRIP events/number in group	OxGRIP events/number in group	Unadjusted Odds Ratio (95%CI)	Adjusted Odds Ratio (95%CI)
Primary Outcomes				
Extended perinatal mortality (n, per 1,000 total births	32/18636 (1.7/1000)	23/18631 (1.2/1000)	0.72 (0.42 – 1.23)	0.53 (0.18 – 1.56) [a,b]
Composite adverse perinatal outcome -1 (CAPO 1) (n, per 1000 total births)	54/18636 (2.9/1000)	36/18631 (1.9/1000)	0.67 (0.44 – 1.02)	0.71 (0.31 – 1.63) [a,c,d]
Expedited birth - pre-labour caesarean section or induction (n, %)	6564/18636 (35.2)	7026/18631 (37.7)	1.11 (1.07 – 1.16)	0.98 (0.90 – 1.07) [a,e]
Secondary Outcomes				
Composite adverse perinatal outcome -2 (CAPO 2) (n, per 1000 total births) [f]	172/18636 (9.2/1000)	163/18631 (8.7/1000)	0.95 (0.76 -1.17)	1.04 (0.66 – 1.63) [g]
Composite adverse perinatal outcome -3 (CAPO 3) (n, per 1000 total births) [h]	458/18636 (24.6/1000)	399/18631 (21.4/1000)	0.87 (0.76 - 0.99)	1.20 (0.90 – 1.59) [g]
Stillbirth (n, per 1,000 total births)	25/18636 (1.3/1000)	16/18631 (0.9/1000)	0.64 (0.34 – 1.20)	0.33 (0.08 – 1.28) [g]
Perinatal death (n, per 1,000 total births)	31/18636 (1.7/1000)	20/18631 (1.1/1000)	0.64 (0.37 – 1.13)	0.33 (0.10 – 1.14) [g]
Apgar score <7 at 5 minutes (n, %) [i]	194/17940 (1.1)	166/18175 (0.9)	0.84 (0.68 – 1.04)	0.90 (0.58 – 1.39) [g]
Hypoxic Ischaemic Encephalopathy - ≥ Grade II (n, %) [j]	27/18611 (0.2)	15/18615 (0.1)	0.56 (0.30 – 1.04)	0.92 (0.25 – 3.36) [g]
Admission to neonatal unit (NNU) (n,%) [j]	769/18611 (4.1)	845/18615 (4.5)	1.10 (1.00 – 1.22)	1.23 (1.00 – 1.52) [g]

The 7.1% increase in expedited birth (aOR 1.08; 95%CI 1.04-1.14) was due to an increase in both pre-labour caesarean section (10.4% to 12.0%) and induction of labour (24.8% to 25.7%). However, post-OxGRIP, significantly fewer women (19.1% to 17.1%) gave birth at < 39+0 weeks (aOR: 0.82 95%CI; 0.75–0.90), and more gave birth at ≥ 41weeks (aOR: 1.19 95%CI; 1.09-1.29).

We demonstrated that introducing a universal ultrasound for growth restriction has limited impact on mortality and severe morbidity, causing only small increases in intervention and significantly less early term birth.

The management algorithm of “screen positive fetuses” was effective, with no stillbirths in the referred group, but one death that could be attributed to the failure to refer the woman appropriately. The problem was sensitivity, with 19/23 (82.6%) post-intervention deaths having screened negative (false negatives). Part of this may be due to our reliance on categorical cut-offs, rather than continuous variables, for instance a pregnancy where the EFW was on the 11th-centile and the CPR on the 6th would have screened negative. It also reflects the limited predictive value of ultrasound.

The detection of birth weight < 10^{th} centile improved when all markers of growth restriction (deceleration in growth velocity, abnormal Doppler indices) were used.

In conclusion, specificity and the management of ‘screen positives’ is crucial to minimise associated workload and unnecessary intervention. The low sensitivity for adverse perinatal outcomes is not primarily because of poor birth weight (< 10^{th} centile) detection rates. It is likely to be because scan parameters, particularly when assessed only once in pregnancy, are not the only risk factors for adverse outcome: demographic and clinical factors and biomarkers have also been shown to be important [52]. This points to the need for predictive models, and using continuous values rather than threshold 'cut offs'.

Detection of LGA neonates

Large-for-gestational age (LGA) is defined as an infant with a birth weight greater than the 90th percentile for the given week of pregnancy. LGA infants are at higher risk of morbidity, including shoulder dystocia and brachial plexus injury [53], as well as mortality, including both antepartum stillbirth and delivery-related perinatal death [54]. Until recently, there has been no direct evidence for a beneficial effect of induction of labour [55]; however, a randomized controlled trial published in 2015 suggested that early induction of labour (between 37^{+0} and 38^{+6} weeks' gestation) for ultrasonically suspected LGA reduced a composite of shoulder dystocia and perinatal morbidity by about 70% without increasing the risk of caesarean section [56].

Sovio et al [57] demonstrated that universal ultrasonography when compared to selective ultrasonography increased the detection rate of LGA infants from 27% to 38%, and that ACGV can help further stratify the risk within this group, distinguishing those with at higher risk for neonatal complications (accelerated ACGV) from those with normal ACGV.

LGA fetuses with increased ACGV had a relative risk of any neonatal morbidity that was twice as high as normal (RR = 2.0; 95% CI, 1.1–3.6; P=0.04); and a risk of severe adverse neonatal outcome that was even more significant (RR: 6.5; 95% CI, 2.0–21.1; P=0.01). Interestingly, the association between an ultrasound diagnosis of fetal overgrowth and neonatal morbidity was not solely attributed to the mechanical difficulties related to shoulder dystocia during birth. Instead, other factors such as poor glycaemic control and their impact on placental function seem to mediate this association [58].

The specificity was high for both approaches, but was slightly higher for selective compared with universal ultrasonography (99% vs 97%, respectively). Women having clinically indicated scans were more likely to have LGA babies as they had higher BMI and higher incidence of pre-existing or gestational diabetes.

The area under the receiver–operating characteristics curve (AUC) for LGA detected by selective ultrasonography was 0.72 and the AUC for that by universal ultrasonography was 0.87 (P<0.0001).

On the basis of these results, it appears clear that universal ultrasonographic screening would slightly increase the detection of LGA infants, however a significant number of LGA infants would remain undetected (almost 2 in 3). It would also substantially increase the number of false positive results leading to unnecessary interventions. For this reason, the authors suggested using ACGV acceleration as a marker to identify LGA neonates at risk of adverse outcomes for which early intervention may be beneficial.

Khan et al [38] demonstrated that EFW > 90th percentile at 35^{+0} to 36^{+6} weeks' gestation had a modest performance in predicting LGA neonates born at term (65% and 46% for neonates with birth weight > 97th and > 90th percentiles, respectively, at a screen-positive rate of 10%). However, the performance improved for prediction of LGA neonates born ≤ 10 days after the scan (84% and 71% for neonates with birth weight > 97th and > 90th percentiles, respectively, at a screen-positive rate of 11%).

The performance of screening for a LGA neonate achieved by EFW Z-score at 35^{+0} to 36^{+6} weeks was not significantly improved by addition of EFW growth velocity or AC growth velocity. However, the authors did not investigate the ability of these markers in predicting adverse outcomes.

Universal third-trimester scan and LGA detection in Oxford

In Oxford we demonstrated that universal third trimester ultrasonography increased the detection rate of LGA (birth weight > 95th centile) neonates from 26% to 44%.

Neonates with an EFW above the 95th centile were at increased risk of composite adverse outcome 1 (CAO1: admission to NICU, Apgar's <7 at 5 minutes, or arterial cord pH <7.1) (aOR 2.18 [1.69-2.80]) and composite adverse outcome 2 (CAO2: intra-uterine fetal death, neonatal death, or hypoxic ischaemic encephalopathy) (aOR 2.58 [1.05-16.0]). However, babies with an EFW between the 90th and 95th centile had a smaller risk of CAO1 and were not at increased risk of CAO2. All pregnancies with EFW >90th centile were at increased risk of secondary maternal outcomes (induction of labour, CS, postpartum haemorrhage, shoulder dystocia), except for obstetric anal sphincter injury. The risk of adverse maternal outcome was higher with increasing EFW.

Although the risk of shoulder dystocia increased with an EFW above the 90th centile, it was only where the EFW was > 95th centile that serious adverse neonatal outcomes increased. Indeed, in about 70% of neonates affected by severe adverse outcomes, these were unrelated to shoulder dystocia. These findings support the hypothesis that pathological fetal overgrowth and macrosomia might have multiple adverse effects on the fetus, in addition to predisposing to birth injuries [58].

Hypothesis

Main hypothesis

Prediction of perinatal mortality and severe morbidity remain a major problem in high-income settings. Attention focuses on identifying fetuses at risk of adverse outcomes due to impaired placental function. In cases where the fetus is identified as at risk, expedited birth may be necessary to prevent adverse outcomes. This often involves induction of labour or caesarean section before the expected due date.

Early-term birth is associated with an increased risk of infant mortality [32]. This risk needs to be carefully considered when deciding on the timing of delivery. Premature birth, even if it falls within the early-term range, can be associated with impaired cognitive and neurological development in some cases [33-35,59]. Therefore, whilst expedited birth is a principal preventive strategy, it comes with potential risks, and the decision must be carefully weighed to avoid harm.

Using maternal characteristics and various ultrasound-based predictors, such as EFW, growth velocity, and Doppler parameters of placental or fetal circulation, could improve the accuracy of risk prediction and reduce unnecessary interventions.

Specific hypothesis

1. Many SGA fetuses are merely constitutionally small and therefore probably not at increased risk; equally, a fetus may have impaired growth or placental function (FGR) but not have an estimated fetal weight below the 10th centile. Curtailment of pregnancy 3 weeks before term should prevent later stillbirth, whether or not the fetus is SGA. However, this has to be balanced with the risks of obstetric intervention, possibly increased infant mortality, potentially greater neonatal unit admission rate and even long-term morbidity.

   Risk stratification of SGA fetuses using multiple parameters, such as EFW, cerebroplacental ratio (CPR), uterine artery Doppler, and pregnancy-associated plasma protein – A (PAPP-A) could allow conservative management for fetuses considered at low risk, leading to fewer interventions and less neonatal morbidity.

2. Assessment of abdominal circumference growth velocity (ACGV), defined as Z-score difference between 20 and 36 week scans, could help in identifying FGR fetuses, which are those at highest risk for adverse outcome.

3. Growth restriction is a complex condition with multiple etiological factors that determine its risk and consequences. Fetuses without “abnormal” (chromosomal abnormality, structural abnormality or infection) SGA or IUGR are presumed to be constitutionally SGA. Although SGA fetuses with Doppler alterations have a worse perinatal outcome [39], constitutionally SGA fetuses also have a higher risk of poor perinatal and long-term outcomes when compared with appropriate-for-gestational-age (AGA) fetuses [60].

   Fetal growth can be affected by various pathological conditions during gestation, such as congenital anomaly, second- or third-trimester haemorrhage, gestational diabetes, and preterm birth which may increase the risk of adverse outcome in SGA fetuses with normal Doppler indices.

   We hypothesize that considering clinical characteristics in addition to ultrasound findings could improve risk stratification and decision-making for management of SGA fetuses.

4. Increased fetal size appears to correlate with increased risk of adverse outcomes. The use of EFW has moderate sensitivity and specificity for size at birth, and poor predictive value for adverse outcomes. Especially in pregnancies complicated by diabetes, the identification of which large fetuses are at most risk is even less clear.

Assessment of abdominal circumference growth velocity (ACGV) and CPR could allow identification of large fetuses at increased risk of adverse outcomes in pregnancy complicated by diabetes.

5. Umbilical artery (UA) Doppler velocimetry is a well-established parameter for the identification of SGA fetuses are increased risk of adverse outcomes, including perinatal mortality. However, a common clinical problem is where the fetus is not SGA, but the UA Doppler is nevertheless abnormal. It is generally believed that the degree of impedance to blood flow in the umbilical artery reflects the degree of placental dysfunction, and so it is biologically plausible to believe these fetuses may also be at increased risk of adverse outcomes. However, the management of such cases is unclear because the prognosis is largely unknown.

   We hypothesize that appropriate-for-gestational-age (AGA) babies with an incidental finding of raised UA pulsatility index (PI) are at increased risk of adverse outcomes compared with AGA babies where the UA PI is normal.

Objectives

Main objective

To investigate the performance of several maternal characteristics and ultrasound markers in predicting perinatal morbidity and mortality in three high risk cohorts (SGA, LGA and AGA with raised umbilical artery pulsatility index).

Specific objectives

1. To assess the clinical impact on obstetric and perinatal outcomes of a risk-stratification protocol in which low-risk SGA fetuses were managed expectantly beyond 37 weeks.

2. To investigate the relationship of fetal ACGV with EFW and CPR as predictors of perinatal outcome in SGA fetuses and determine whether use of ACGV, in addition to EFW and CPR, improves the prediction of adverse outcome.

3. To evaluate whether clinical phenotypes of SGA fetuses can be identified and used for adverse perinatal outcome risk stratification to facilitate clinical decision-making.

4. To assess the role of ACGV and CPR as markers of placental function, in predicting adverse perinatal outcome in pregnancies with gestational diabetes or pre-existing diabetes (type 1 - 2).

5. To determine if appropriate-for-gestational-age (AGA) fetuses – those that are not SGA – with a raised (> 95^{th} centile) UA PI in the early third trimester are at increased risk of placental dysfunction and adverse outcome.

SGA cohort

Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol

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Introduction

The small-for-gestational-age (SGA) fetus is at increased risk of perinatal complication, including stillbirth [41,61-63] .Its identification remains a cornerstone of antenatal care. Several authors report improved outcome of such babies if they are identified in utero, largely as result of expedited delivery [64,65], although this is still a matter of debate [66-68]. Although the DIGITAT study [69] and subsequent Cochrane review [70] concluded that intervention did not alter perinatal outcome, or indeed caesarean section rate, these studies were underpowered to detect an impact on stillbirth rate.

On this basis, the current UK guidelines recommend delivery at 37 weeks for all fetuses with an estimated fetal weight (EFW) below the 10th centile, even when the pregnancy is otherwise uncomplicated and fetal/placental Doppler findings are normal; USA guidelines are less prescriptive and there is uncertainty regarding optimal management and timing of delivery [71]. A principal difficulty is that many SGA fetuses are merely constitutionally small and therefore probably not at increased risk; equally, a fetus may have impaired growth or placental function (fetal growth restriction (FGR)) but not have fetal weight below the 10th centile [40,72,73]. Curtailment of pregnancy 3 weeks before term should prevent later stillbirth, whether or not the fetus is SGA. However, this has to be compared with the risks of obstetric intervention, possibly increased infant mortality [32], potentially greater neonatal unit (NNU) admission rate [66] and even long-term morbidity [33,34].

Recent data suggest that the risk of adverse outcome can be better determined using multiple factors, including the cerebroplacental ratio (CPR) [74], and that conservative management of SGA fetuses with normal parameters is reasonable [75]. Delivery at 37 weeks for SGA was recommended at our unit before 2014 when we introduced a protocol that included conservative management beyond 37 weeks of SGA babies not considered FGR.

The aim of this study was to compare the impact of this protocol with historical data to determine its effects on obstetric and perinatal outcomes of babies diagnosed antenatally as SGA.

Methods

This is an impact study examining data collected over a 39-month period (1 January 2013 to 30 April 2016). The study was conducted at the John Radcliffe Hospital, Oxford, UK, a large tertiary referral unit with > 8000 deliveries per annum. Throughout the duration of the study, growth scanning was not routine, being performed according to risk factors and abdominal palpation.

Eligible women were those referred to the Fetal Medicine Unit (FMU) with a singleton non-anomalous fetus diagnosed antenatally as SGA from 36+0 weeks of gestation, but with normal umbilical artery (UA) Doppler pulsatility index (PI) prior to referral. SGA was defined as EFW < 10th centile, calculated using Hadlock charts [46]. Protocol-based management of SGA pregnancies was introduced on 1 October 2014, with a dedicated clinic for those pregnancies. Institutional Review Board approval for data collection was granted.

The pre-protocol group consisted of women referred to the FMU between January 2013 and September 2014, and who were managed in an ad-hoc manner according to clinicians' preferences, based broadly on the national guidelines, which recommend delivery at 37 weeks.

The protocol group consisted of women referred from October 2014 to April 2016, who were managed in accordance with the following protocol. On the first appointment, gestational age (GA) was confirmed based on first-trimester crown – rump length (CRL) measurement. Maternal serum level of pregnancy-associated plasma protein-A (PAPP-A) and second-trimester uterine artery (UtA) Doppler were reviewed when available. Blood pressure (BP) and urine were also assessed. Ultrasound measurements were retaken, UA-PI and middle cerebral artery (MCA) PI were measured and CPR was calculated.

All examinations were performed by an experienced operator (M.V. or A.C.) using a Voluson E8 (GE Medical Systems, Zipf, Austria) machine, equipped with a 6 – 2-MHz linear curved-array transducer. The amniotic fluid volume was assessed, measuring the deepest vertical pool. The UA was examined at a free-floating portion of the umbilical cord. MCA was measured in a transverse view of the fetal head, at the level of its origin from the circle of Willis. CPR was calculated as the ratio of MCA-PI to UA-PI, and was considered abnormal when < 5^{th} centile for GA [76]. Doppler recordings were performed in the absence of fetal movements and voluntarily suspended maternal breathing. All pulsed Doppler parameters were recorded automatically from at least three consecutive waveforms, with the angle of insonation as close to 0 degree as possible and always below 30 degree.

Based on EFW, Doppler measurements and risk factors, women managed using the new protocol were stratified and underwent a tailored follow-up and delivery, timed according to the following clinic protocol: delivery, by induction of labour, was advised at 37+0 weeks, and not before, in ‘high-risk’ babies, defined as EFW < 3rd centile, CPR < 5th centile, mean UtA-PI at the anomaly scan > 95th centile [77], PAPP-A < 0.3 multiples of the median (MoM) in the first trimester or pregnancy-induced hypertension (≥140/90 mmHg).

If the above risk factors were absent (‘low-risk’ babies), the ultrasound examination was repeated in 1 week if EFW was between the 3rd and 5th centiles, or in 2 weeks if it was between the 5th and 10th centiles. When EFW was between the 3rd and 5th centiles, patients were advised to deliver by 40+0 weeks; when it was between the 5th and 10th centiles, delivery was recommended by 41+0 weeks.

Ultrasound and pregnancy outcomes were compared between the two periods. Ultrasound data were collected retrospectively for the pre-protocol group and prospectively for the protocol group, via an electronic database system (Viewpoint); these were merged with demographic and obstetric details, as well as neonatal outcomes, via electronic patient record systems (Cerner Millenium and Badger). The last evaluation, performed within 1 week of delivery, was considered for analysis.

The primary outcome was neonatal composite adverse outcome (NCAO), defined as the presence of at least one of the following: intrauterine or neonatal death; Apgar score < 7 at 5min; cord arterial pH < 7.10; hypoglycaemia (blood glucose < 2.5 mmol/L); and need for ventilation or cooling. Secondary outcomes were admission to the NNU, GA at delivery, mode of delivery and caesarean section rate. Neonatal policy remained unchanged during the time period of the study and there was no policy for automatic NNU admission based simply on GA or birth weight.

Statistical analysis

Interventions and outcomes were compared between the two groups and according to the risk stratification described above. Categorical variables are presented as n (%). Chi-square or Fisher's exact tests were performed for categorical variables, and odds ratios (ORs) with 95% CI were calculated; the independent sample t-test was used for continuous variables.

Results

During the 39-month study period when data were collected, 363 women attended the FMU at the John Radcliffe Hospital having had at least one scan showing a non-anomalous fetus with EFW < 10^{th} centile for GA after 36 weeks: 185 (51%) between January 2013 and September 2014 and 178 (49%) between October 2014 and April 2016. These represented 1.6% and 1.8%, respectively, of singleton pregnancies > 36 weeks delivered during this time at the John Radcliffe Hospital.

After exclusion of fetuses with EFW > 10^{th} centile (22 in the pre-protocol group and 35 in the protocol group) and those without follow-up data (25 in the pre-protocol group), there were 138 (49%) pregnancies in the pre-protocol group and 143 (51%) in the protocol group.

Maternal baseline characteristics are shown in Table 1. There were no significant differences between pre-protocol and protocol groups. There were also no significant differences in the incidence of risk factors for SGA.

Risk stratification is summarized in Table 2. There were no significant differences between pre-protocol and protocol groups, although there was a trend toward a greater proportion of high-risk pregnancies in the pre-protocol group.

Table 1 Maternal baseline characteristics of singleton pregnancies complicated by small-for-gestational-age (SGA) fetus, according to whether they were managed with delivery at 37 weeks (pre-protocol group) or by expectant management following risk stratification (protocol group)

Characteristic	*Pre-protocol (n = 138)*	*Protocol (n = 143)*	P
Age (years)	28.24 ± 5.76	29.58 ± 5.76	0.63
BMI (kg/m^2)	24.1 ± 5.69	23.6 ± 4.5	0.36
Nulliparous	69 (50)	69 (48)	0.16
Hypertensive disorder	11 (8.0)	11 (7.7)	0.70
Gestational diabetes	7 (5.1)	6 (4.2)	0.60
Smoker	16 (11.6)	26 (18.2)	0.23
Drug misuse	5 (3.6)	5 (3.5)	0.82
Previous SGA baby	20 (14.5)	34 (23.8)	0.10

Data are given as mean ± SD or *n* (%). BMI, body mass index.

Table 2 Characteristics and corresponding risk stratification of singleton pregnancies complicated by small-for-gestational-age fetus, according to whether they were managed with delivery at 37 weeks (pre-protocol group) or by expectant management following risk stratification (protocol group)

Risk stratification/characteristic	*Pre-protocol (n = 138)*	*Protocol (n = 143)*	P
High risk*	81 (58.7)	69 (48.3)	0.08
EFW ≤ 3rd centile	54 (39.1)	47 (32.9)	0.22
CPR < 5th centile	30 (21.7)	25 (17.5)	0.18
Mean UtA-PI > 95th centile†	15/43 (35)	14/50 (28)	0.5
PAPP-A < 0.3 MoM	6 (4.3)	8 (5.6)	0.4
Low risk	57 (41.3)	74 (51.7)	0.08
3rd < EFW ≤ 5th centile	30 (21.7)	36 (25.2)	0.5
5th < EFW < 10th centile	27 (19.6)	38 (26.6)	0.17

Data are given as *n* (%). *Inclusion criteria not mutually exclusive. †Not all women had second-trimester uterine artery (UtA) Doppler. CPR, cerebroplacental ratio; EFW, estimated fetal weight; MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index.

Maternal outcomes are shown in Table 3. In the protocol group, the rates of induction of labour and caesarean section were lower, and rate of vaginal delivery higher than in the pre-protocol group.

Table 3 Maternal outcomes of pregnancies complicated by small-for-gestational-age fetus, according to whether they were managed with delivery at 37 weeks (pre-protocol group) or by expectant management following risk stratification (protocol group)

Outcome	*Pre-protocol* (n = 138)	*Protocol* (n = 143)	OR (95% CI)	P
Vaginal delivery	83 (60.1)	118 (82.5)	3.13 (1.80–5.42)	< 0.01
Instrumental delivery	15 (10.9)	17 (11.9)	1.11 (0.53–2.31)	0.79
Labor induction	91 (65.9)	77 (53.8)	0.60 (0.37–0.98)	0.04
Elective LSCS	31 (22.5)	17 (11.9)	0.47 (0.24–0.89)	0.02
Emergency LSCS	24 (17.4)	18 (12.6)	0.68 (0.35–1.33)	0.26

Data are given as *n* (%). LSCS, lower segment Cesarean section; OR, odds ratio.

Overall neonatal outcomes are shown in Table 4. GA at delivery and birth weight were significantly higher in the protocol group. Although no significant difference was observed between the two groups of neonates in terms of Apgar score, umbilical arterial pH or base-excess alone, the incidence of NNU admission was higher, and NCAO more than twice as common in the pre-protocol group than in the protocol group.

Table 4 Neonatal outcomes of pregnancies complicated by small-for-gestational-age fetus, according to whether they were managed with delivery at 37 weeks (pre-protocol group) or by expectant management following risk stratification (protocol group)

Outcome	*Pre-protocol* (n = 138)	*Protocol* (n = 143)	OR (95% CI)	P
Birth weight (g)	2328 ± 335	2544 ± 337		< 0.01
Perinatal mortality	1 (0.7)	1 (0.7)	1.09 (0.07–17.67)	1.00
GA at delivery (weeks)	37.4 ± 1.7	38.2 ± 1.9		0.04
Delivery ≥39 weeks	27 (19.6)	50 (35.0)	2.28 (1.33–3.94)	< 0.01
Arterial pH < 7.1	4/51 (7.8)	1/47 (2)	0.26 (0.03–2.37)	0.36
Arterial pH	7.25 ± 0.09	7.25 ± 0.08		0.77
Hypoglycemia	14/121 (11.6)	11/119 (9.2)	0.78 (0.34–1.79)	0.51
5-min Apgar < 7	3 (2.2)	0 (0)		
NNU admission	54 (39.1)	18 (12.6)	0.22 (0.12–0.41)	< 0.01
Assisted ventilation	20 (14.5)	8 (5.6)	0.32 (0.14–0.76)	< 0.01
Total days in NNU	268 ± 1.94	152 ± 1.06		0.07
NCAO	30 (21.7)	13 (9.1)	0.36 (0.18–0.72)	< 0.01

Data are given as mean ± SD, *n* (%) or *n/N* (%). GA, gestational age; NCAO, neonatal composite adverse outcome; NNU, neonatal unit; OR, odds ratio.

ORs with 95% CI for the main maternal and neonatal outcomes for the protocol group with the pre-protocol group as reference are shown in Figure 1.

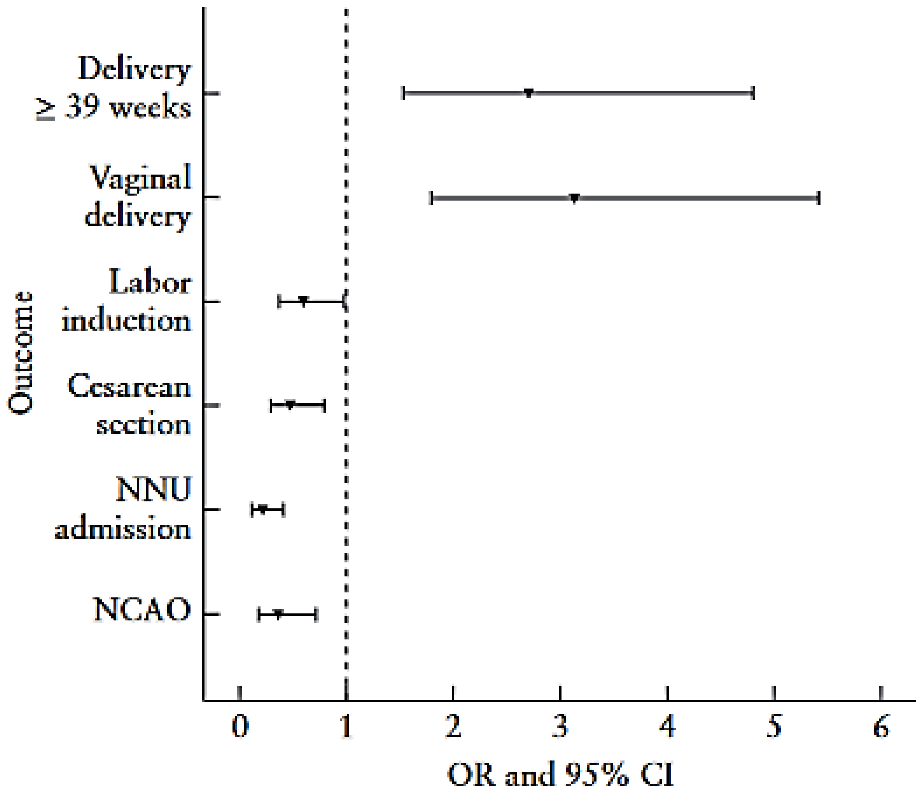

Figure 1 Plot of odds ratios (OR) with 95% CI for risk of main maternal and neonatal outcomes for pregnancies complicated by small-for-gestational-age (SGA) fetus managed expectantly following risk stratification, with SGA group managed by delivery at 37 weeks as reference (dashed line). NCAO, neonatal composite adverse outcome; NNU, neonatal unit.

Table 5 shows data obtained following stratification of interventions and major outcomes according to the allocated risk level. High-risk babies encompassed 58.7% of babies in the pre-protocol group and 48.3% of babies in the protocol group. In low-risk SGA babies, GA at delivery was slightly but significantly higher, rate of spontaneous onset of labour was significantly higher and birth weight significantly greater, in the protocol group compared with the pre-protocol group. The low incidence of NCAO in these babies was not significantly altered, but NNU admission rate was significantly reduced in the protocol group. In high-risk SGA babies, there were largely non significantly lower intervention rates, significantly higher mean birth weight and significantly lower incidence of NNU admission and NCAO in the protocol group. There was one intrauterine death (IUD) in each group. In the pre-protocol group, it occurred at 37+2 weeks, and was diagnosed at the first FMU appointment; birth weight was < 3rd centile. In the protocol group, a fetal death occurred in a pregnancy first identified as SGA at 38 weeks; EFW was on the 3rd centile and CPR was abnormal. Elective caesarean section was scheduled because of a previous caesarean section but was delayed by 3 days. IUD was diagnosed the day before planned delivery.

Table 5 Major interventions and outcomes, stratified according to risk category, of pregnancies complicated by small-for-gestational-age fetus managed with delivery at 37 weeks (pre-protocol group) or expectantly following risk stratification (protocol group)

Risk category and intervention/outcome	*Pre-protocol (n = 138)*	*Protocol (n = 143)*	*OR (95% CI)*	P
High-risk	81 (58.7)	69 (48.3)		
GA at delivery (weeks)	37.0 ± 1.3	37.6 ± 1.2		0.01
GA at delivery > 39 weeks	7 (8.6)	8 (11.6)	1.39 (0.48–4.04)	0.36
Birth weight (g)	2173 ± 294	2355 ± 342		< 0.01
Spontaneous labor	3 (3.7)	11 (15.9)	4.93 (1.32–18.5)	0.01
Induction of labor	52 (64.2)	42 (60.9)	0.86 (0.45–1.68)	0.67
Elective LSCS	23 (28.4)	14 (20.3)	0.64 (0.3–1.37)	0.25
Emergency LSCS	18 (22.2)	9 (13.0)	0.52 (0.21–1.26)	0.15
NCAO	22 (27.2)	9 (13.0)	0.39 (0.16–0.92)	0.03
NNU admission	38 (46.9)	16 (23.2)	0.34 (0.17–0.69)	< 0.01
Low-risk	57 (41.3)	74 (51.7)		
GA at delivery (weeks)	38.4 ± 1.17	39.1 ± 1.25		< 0.01
GA at delivery >39 weeks	20 (35.1)	42 (56.8)	2.43 (1.19–4.95)	0.01
Birth weight (g)	2573 ± 237	2720 ± 321		< 0.01
Spontaneous labor	9 (15.8)	34 (45.9)	4.53 (1.95–10.57)	< 0.01
Induction of labor	39 (68.4)	35 (47.3)	0.41 (0.20–0.85)	0.02
Elective LSCS	8 (14.0)	3 (4.1)	0.26 (0.07–1.03)	0.06
Emergency LSCS	6 (10.5)	9 (12.2)	1.18 (0.39–3.52)	0.77
NCAO	8 (14.0)	4 (5.4)	0.35 (0.10–1.23)	0.09
NNU admission	16 (28.1)	2 (2.7)	0.07 (0.02–0.33)	< 0.01

Data are given as *n* (%) or mean ± SD. GA, gestational age; LSCS, lower segment Cesarean section; NCAO, neonatal composite adverse outcome; NNU, neonatal unit; OR, odds ratio.

Discussion

There is an increasing trend toward early-term delivery of SGA babies [77]. Term NNU admission rate is increasing in many countries [78]; early-term delivery, which is also increasing in an attempt to prevent stillbirth, may be a major risk factor.

Our data suggest that a prescriptive protocol for management, including risk stratification with conservative management for those considered at low risk, allows fewer interventions to be accompanied by less neonatal morbidity. The data suggest that, in the pre-protocol time period, there was already some risk stratification for babies that would have been lower risk. These babies were not all being delivered, as UK guidelines recommend, at 37 weeks. In some instances, this is because they were not identified until after 37 weeks. If they had been identified earlier, the differences in intervention rates between the two groups would have been greater.

Nevertheless, a more conservative protocol-based management allowed significantly more pregnancies to reach 39 weeks, to go into labour spontaneously and, when delivery was considered indicated, to not be delivered by caesarean section. This was followed by a considerable reduction in NNU admission, although there was no alteration in the rate of NCAO which, in these ‘low-risk’ babies, was relatively rare. Although the numbers are too small to make conclusions about perinatal mortality, this does suggest that reduced intervention in SGA babies that are likely to be constitutionally small is reasonable and may even improve outcome.

For babies considered high risk, there are also improvements in neonatal outcome. The data do not allow firm conclusions as to why, and it is possible that the babies in the pre-protocol group were simply higher risk. However, the observed improvements in neonatal outcome were not because of a difference in the incidence of detected SGA between the two groups (which was 1.6% for the pre-protocol group and 1.8% for the protocol group). These percentages are in accordance with expectations: approximately 5% of our babies have EFW < 10^{th} centile according to Hadlock charts and detection rates of SGA in the UK are around 30% [65].

Indeed, the differences could also be related to the protocol stipulating induction as opposed to caesarean section, no earlier than 37 weeks, even in these higher-risk babies. The IUD in the protocol group was of a fetus whose condition was diagnosed late, but met criteria for expedited delivery. Thus, this IUD would have occurred even under the former protocol. This highlights the need for identification of SGA, and of FGR among non-SGA babies, which was not the intention of this protocol. Previous reports have shown variable or increased morbidity with earlier delivery [66-68]. This, particularly with respect to NNU admission, is to be expected if SGA, but otherwise healthy, babies are delivered even mildly preterm. The risk-stratification part of the protocol, attempting to differentiate between constitutionally small fetuses and FGR fetuses, was an adaptation of a published protocol [79], although we delayed induction of labour to 41 weeks in babies considered at least risk. This was because a key aim of our protocol was to limit induction of labour, and the GA window of 40 – 41 weeks is one in which a large number of women should deliver spontaneously. Other risk factors that may help to determine risk in SGA babies include UtA Doppler in the third trimester [80], abdominal circumference trajectory [39] and maternal age [81]. Using these may further reduce the risk of serious adverse outcome; ideally, modelling of independent risk factors would allow a risk-assessment tool.

Our data also suggest that the introduction of protocol-based management may improve maternal outcome. This is in contrast with the conservatively managed arm of DIGITAT [69]. Although routine induction of labour at 39 weeks has not been shown to increase intrapartum intervention in many randomized controlled trials (RCTs) of higher-risk pregnancies, overall caesarean section rate is often very high [82] and induction is not viewed well by women [83].

We acknowledge a number of limitations. As discussed, we cannot exclude the possibility that, despite similar demographics, incidence of risk factors and detection rate of SGA babies, improved neonatal outcome in the babies considered high risk is because the pre-protocol group contained higher-risk babies. This does not, however, prevent conclusions from being drawn about the low-risk babies. Whilst it highlights the drawbacks of an impact study, a RCT [69] that addressed early-term delivery did not use a prescriptive risk-stratification protocol like ours. Our findings are also limited by the retrospective nature of data collection, particularly in the pre-protocol group, and the consequential missing outcomes. Finally, we are unable to draw conclusions about stillbirth and long-term morbidity; to do this would require vast numbers. The potential benefit of early-term labour is prevention of later stillbirth. Indeed, curtailment of a pregnancy at any gestation will prevent stillbirth beyond the GA of delivery, so this outcome cannot be considered in isolation; at the very least, neonatal and infant mortality must be considered.

Late-onset FGR is also associated with increased perinatal morbidity in the form of fetal distress, hypoglycaemia, seizures, behavioural problems, cerebral palsy and cardiovascular disease [84-86]. There are, however, other potential risks, including increased NNU admission [66], childhood morbidity [33,34] and 'medicalization'. What are not clear are the respective roles of GA at delivery, birth weight or pregnancy characteristics associated with early-term delivery. The ACOG Practice Bulletin [87] states: 'Size alone is not an indication of a complication. As a result of this confusion, under-intervention and over-intervention can occur'. The prevention of over-intervention will become even more important if, as has been recommended in the UK [88], detection rates of SGA increase. This means that risk stratification, shown in the current study to be effective, is essential. Although this study was too small to demonstrate an effect on stillbirth, it is uncertain if a large reduction in near-term stillbirth is achievable by routine delivery of small babies, even if they are identified. A version of the protocol that we have described in all pregnancies might yet achieve this.

Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term small-for-gestational-age fetuses

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Introduction

Stillbirth is a devastating pregnancy outcome occurring in up to 1% of pregnancies in the developed world [89]. Accumulating data suggest that fetal growth restriction (FGR) is a major determinant of perinatal mortality and morbidity [89,90] in particular stillbirth [91,92]. FGR is also associated with an increased risk of adult chronic disease, such as coronary heart disease, stroke, hypertension, non-insulin-dependent diabetes [93] and neurocognitive dysfunction [94].

Small-for-gestational age (SGA), defined as fetal weight/birth weight below the 10th centile for gestational age, is commonly used as a proxy for FGR [87]. However, many SGA fetuses are physiologically small and have reached their appropriate growth potential on the basis of genetic, placental, maternal and environmental factors [95].Therefore, the interchangeable use of the terms FGR and SGA is incorrect and the ability to detect FGR fetuses among the SGA population, and even among the appropriately grown (appropriate-for-gestational age, AGA) population, is important in order to prevent unnecessary intervention and iatrogenic preterm birth.

Multiple markers for FGR have been investigated, including ultrasound, biophysical and even biochemical factors, and integrated into predictive models [75,96]. These studies have demonstrated the predictive value of estimated fetal weight (EFW), uterine artery Doppler and particularly the cerebroplacental ratio (CPR) [75,96]. However, assessment of abdominal circumference growth velocity (ACGV) can also identify SGA neonates at highest risk for adverse outcome [39,97,98]. Although reduced ACGV is associated with low EFW and CPR [97], it is not clear whether it is independent of these markers and whether it can be used in conjunction with them to improve the prediction of adverse outcome.

The aim of this study was to investigate the relationship of fetal ACGV with EFW and CPR as predictors of perinatal outcome in SGA fetuses and determine whether use of ACGV, in addition to EFW and CPR, improves the prediction of adverse outcome.

Methods

This was a cohort study conducted at the John Radcliffe Hospital, Oxford, UK, a large teaching hospital with more than 8000 deliveries per annum. Growth scanning in the third trimester of pregnancy was performed according to risk factors and serial measurement of the symphysis – fundal height, as per local and national guidelines [6,99]. Women referred to the Fetal Medicine Unit with a singleton pregnancy diagnosed antenatally as SGA (EFW < 10th centile using Hadlock charts [46]) from 36+0 weeks' gestation were eligible for inclusion.

Exclusion criteria were multiple pregnancy, abnormal karyotype, missing data on first-trimester dating, and life-limiting fetal abnormalities or those requiring neonatal surgery. The scan performed between 36+0 and 38+0 weeks' gestation for each fetus was included in the analysis.

Gestational age (GA) was confirmed based on first-trimester crown – rump length (CRL) at the time of the nuchal scan [100]. Fetal biometry was measured according to INTERGROWTH-21st standards [101]. Umbilical artery (UA) pulsatility index (PI) was calculated from a free-floating portion of the umbilical cord. Middle cerebral artery (MCA)-PI was measured in a transverse view of the fetal head, at the level of its origin from the circle of Willis [102], and the CPR was calculated as the ratio MCA-PI/UA-PI [76]. Doppler recordings were performed according to the 'Doppler quality criteria' used in the INTERGROWTH-21st

Project [101]. ACGV centiles for this cohort were calculated using, as a reference range, data from a large unselected population of 3334 fetuses followed at this unit, obtained after the introduction of a routine 36-week growth scan. These data were extracted and modelled separately for 19 – 21 and 36 – 38 weeks in order to produce locally fitted Z-scores. The ACGV was defined as the Z-score difference between the 19 – 21- and 36 – 38-week scans, divided by the interval in days between the two ultrasound evaluations and multiplied by 10022.

The EFW was expressed as a centile according to Hadlock et al. [46]. The CPR was expressed as a centile for gestational age according to Baschat – Gembruch charts [76]. Established cut-offs of EFW [47], ACGV [103] and CPR [76] were used.

All ultrasound examinations were performed by two experienced operators (A.C. or M.V.) using a VolusonE8 (GE Medical Systems, Zipf, Austria) machine, equipped with a 6 – 2-MHz linear curved-array transducer. Both sonographers underwent training and performed standardization exercises. Their performance was also monitored by a comprehensive package of quality control for ultrasonographic data collection in fetal biometry according to the INTERGROWTH-21st Project [16].

Pregnancies with EFW < 10th centile were either delivered or managed conservatively with close follow-up, as described elsewhere [47]. Composite adverse outcome 1 (CAO-1) was defined, in accordance with a recent paper demonstrating the value of ACGV as a predictor of adverse outcome [39], as one or more of the following criteria: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to the neonatal unit. A second composite adverse outcome (CAO-2) also included hypoglycaemia (blood glucose < 2.5 mmol/L), intrapartum fetal distress requiring expedited delivery and perinatal death.

Data were collected prospectively from the hospital electronic database of ultrasonography (ViewPoint, GE Healthcare), electronic patient record (Cerner Millennium, London, UK) and electronic record system for neonatal unit care (Badgernet, Clevermed, Edinburgh, UK), and merged postnatally.

Univariate logistic regression analysis using continuous and binary variables was performed as a preliminary analysis to establish which of the adverse outcome measures were related significantly to ACGV, EFW and CPR. Simple correlation confirmed that there is no problem of co-linearity with these predictors. Multivariate simultaneous entry logistic regression analysis was then performed, using as binary variables the three considered predictors: ACGV < 10^{th} centile, EFW < 3^{rd} centile and CPR < 5^{th} centile. For each outcome, the regression model included the factors that were significant predictors in univariate analysis. In order to determine the performance of ACGV in predicting adverse outcome, three combinations of predictors were analysed: (1) EFW with CPR, (2) ACGV alone, and (3) EFW, CPR and ACGV together. Initially these were analysed as continuous variables, using a statistical model to calculate the probability of developing adverse outcome [104]. For this purpose, binary logistic regression analysis was performed using each target predictor for each adverse outcome. The intercept and regression coefficient for each variable were obtained. The following equation was then used to calculate the risk of adverse outcome [104]: Fetus risk = exp(fetus risk score)/[1+exp(fetus risk score)]×100, where fetus risk score = intercept + (regression coefficient $variable_1$×$variable_1$) + (regression coefficient $variable_n$×$variable_n$).

Areas under the receiver – operating characteristics curves (AUC) with 95% CI were calculated. The three predictors were then analysed as binary variables for clinical applicability. These were: (1) EFW < 3^{rd} centile or CPR < 5^{th} centile, (2) ACGV < 10^{th} centile of the reference range (ACGV < −1.3091) alone, and (3) EFW < 3^{rd} centile or CPR < 5^{th} centile or ACGV < 10^{th} centile. The sensitivity and specificity were calculated, with positive and negative likelihood ratios (LRs), for all adverse outcomes. Percentage occurrence or measures of central tendency were calculated for all variables of interest.

Statistical analysis was carried out using SPSS version 22 (IBM Corp., Armonk, NY, USA). Institutional review board approval was obtained (27 July 2017, REC17/SC/0374).

Results

A total of 249 women with a singleton pregnancy attended the Fetal Medicine Unit at the John Radcliffe Hospital between October 2014 and July 2016, having had a scan showing an EFW < 10^{th} centile between 36+0 and 38+0 weeks. Of these, five women were excluded because of fetal abnormality, three because re-measurement showed EFW to be > 10^{th} centile and six because follow-up data were not obtainable. Therefore, 235 pregnancies diagnosed as SGA were examined. Maternal baseline characteristics are shown in Table 1.

Table 1 Baseline characteristics of 235 women with small-for-gestational-age (SGA) fetus at 36–38 weeks' gestation included in study cohort

Characteristic	*Value*
Maternal age (years)	29.8 ± 5.99
Body mass index	
< 18.5 kg/m²	17 (7.2)
18.5–24.9 kg/m²	132 (56.2)
25.0–29.9 kg/m²	58 (24.7)
30.0–34.9 kg/m²	23 (9.8)
35.0–39.9 kg/m²	4 (1.7)
> 40 kg/m²	1 (0.4)
Nulliparous	115 (48.9)
Maternal ethnicity	
Caucasian	163 (69.4)
Afro-Caribbean	4 (1.7)
Asian	36 (15.3)
Mixed	32 (13.6)
Cigarette smoker	45 (19.1)
Alcohol abuse	3 (1.3)
Drug abuse	9 (3.8)
Essential hypertension	8 (3.4)
Pre-eclampsia	14 (6.0)
Prepregnancy disease	100 (42.6)
Diabetes (Type 1 or Type 2)	0 (0)
Gestational diabetes	15 (6.4)
Previous stillbirth	3 (1.3)
Previous SGA	60 (25.5)
In-vitro fertilization pregnancy	12 (5.1)

Data are presented as mean ± SD or *n* (%).

Mean gestational age of the study cohort was 256.8 ± 4.67 days. Mean interval between the third-trimester ultrasound scan and delivery was 10.3 ± 12 days. Mean EFW of the study cohort was 2262 ± 206 g and 51 (21.7%) cases had EFW < 3^{rd} centile. At birth, 163 (69.4%) fetuses were SGA according to the INTERGROWTH-21^{st} Project charts [27].

Pregnancy outcomes and ultrasound parameters of the study cohort are shown in Table 2.

Table 2 Delivery characteristics, pregnancy outcome and ultrasound measurements at 36–38 weeks of 235 small-for-gestational-age fetuses included in study cohort

Parameter	*Value*
GA at delivery (days)	267 ± 9.04
Induction of labor	135 (57.4)
Delivery mode	
Spontaneous vaginal delivery	140 (59.6)
Instrumental vaginal delivery	26 (11.1)
Elective Cesarean section	32 (13.6)
Emergency Cesarean section	37 (15.7)
Neonatal sex	
Female	131 (55.7)
Male	104 (44.3)
Birth weight (g)	2481 ± 342.31
Birth weight < 10^{th} centile*	163 (69.4)
Birth-weight centile*	2.69 ± 1.32
Fetal hypoglycemia†	26 (11.1)
5-min Apgar score < 7	2 (0.9)
Arterial cord pH < 7.10	3 (1.3)
Neonatal unit admission	32 (13.6)
Perinatal mortality	1 (0.4)
Composite adverse outcome 1‡	35 (14.9)
Composite adverse outcome 2§	71 (30.2)
EFW at third-trimester scan (g)	2262 ± 206
EFW < 3^{rd} centile¶	51 (21.7)
CPR	1.76 ± 0.54
CPR < 5^{th} centile¶	45 (19.1)
ACGV**	−1.163 ± 1.05
ACGV < 10^{th} centile**	93 (39.6)

There was a significant but not strong correlation between the ACGV and EFW centiles (r=0.25,P=0.001) and between the ACGV and CPR centiles (r=0.22,P=0.001). Univariate analysis using ACGV, EFW and CPR centiles as continuous variables showed that all three markers predicted significantly both CAO-1 and CAO-2 in near-term SGA fetuses.

All three binary variables, EFW < 3rd centile, CPR < 5th centile and ACGV < 10th centile, were associated significantly with both outcomes on univariate analysis, except for EFW < 3rd centile, which did not predict significantly CAO-2 (Table 3).

Table 3 Univariate logistic regression analysis for prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses based on continuous variables abdominal circumference growth velocity (ACGV), estimated fetal weight (EFW) and cerebroplacental ratio (CPR) centiles, and binary variables ACGV < 10^{th} centile, EFW < 3^{rd} centile and CPR < 5^{th} centile

	Odds ratio (95% CI)					
Outcome	*ACGV centile*	*EFW centile*	*CPR centile*	*ACGV < 10^{th} centile*	*EFW < 3^{rd} centile*	*CPR < 5^{th} centile*
CAO-1	2.02 (1.41–2.90)***	1.00 (1.00–1.01)***	1.02 (1.01–1.04)**	2.45 (1.15–5.21)*	2.52 (1.17–5.45)*	3.03 (1.38–6.63)**
CAO-2	1.68 (1.26–2.24)***	1.00 (1.001–1.004)**	1.02 (1.01–1.03)**	2.00 (1.12–3.57)*	1.35 (0.70–2.60)	2.45 (1.25–4.78)**

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death.

Multivariate simultaneous entry logistic regression analysis using as binary variables all risk factors that were significant predictors of adverse outcome on univariate analysis showed that only CPR < 5th centile [adjusted OR (aOR) 2.54 (95% CI, 1.07 – 5.99)] was a significant predictor of CAO-1. For CAO-2, both CPR

< 5^{th} [aOR 2.42 (95% CI, 1.18 – 4.99)] and ACGV <10^{th} centile [aOR 1.95 (95% CI, 1.07 – 3.54)] were significant predictors (Table 4).

Table 4 Simultaneous entry logistic regression analysis for prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses based on binary variables estimated fetal weight (EFW) < 3^{rd} centile, cerebroplacental ratio (CPR) < 5^{th} centile and abdominal circumference growth velocity (ACGV) < 10^{th} centile

Outcome	*Predictor*	*Wald test*	*Adjusted OR (95% CI)*	P
CAO-1	EFW < 3^{rd} centile	2.49	1.95 (0.85–4.48)	0.115
	CPR < 5^{th} centile	4.50	2.54 (1.07–5.99)	0.034
	ACGV < 10^{th} centile	3.68	2.15 (0.98–4.68)	0.055
CAO-2	CPR < 5^{th} centile	5.75	2.42 (1.18–4.99)	0.016
	ACGV < 10^{th} centile	4.77	1.95 (1.07–3.54)	0.029

CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death. OR, odds ratio.

The principal benefit of using ACGV in addition to EFW and CPR for the prediction of adverse outcome in SGA fetuses is the improvement of the negative likelihood ratios (LR−) (Table 5). For CAO-1, LR− was 0.69 (95% CI, 0.49 – 0.99) for EFW <3^{rd} centile or CPR <5^{th} centile, improving to 0.38 (95% CI, 0.18 – 0.80) when ACGV<10^{th} centile was included. For CAO-2, the corresponding LR− values were 0.83 (95% CI, 0.67 – 1.04) and 0.62 (95% CI, 0.41 – 0.93).

AUCs of the three logistic regression models are shown in Table 6 and receiver – operating characteristics curves for both outcomes are shown in Figure 1. At a 50% specificity, corresponding to approximately 50% of SGA fetuses being labelled as 'high risk', the addition of ACGV to EFW and CPR increased the sensitivity for CAO-1 from 71.43% (95% CI, 53.7 – 85.4) to 78.79% (95%CI, 61.1 – 91.0), and for CAO-2 from 68.57% (95% CI,56.4 – 79.1) to 75.76% (95% CI, 63.6 – 85.5).

Table 5 Diagnostic performance of three different predictive models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as binary variables, for the prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses

Predictive model	n (%)	*Sensitivity (%) (95% CI)*	*Specificity (%) (95% CI)*	*PPV (%) (95% CI)*	*NPV (%) (95% CI)*	*LR+ (95% CI)*	*LR− (95% CI)*
CAO-1	35 (14.9)						
EFW < 3rd centile or CPR < 5th centile	17 (48.6)	51.43 (33.99–68.62)	69.90 (62.95–76.23)	23.38 (17.17–30.98)	88.96 (84.99–91.98)	1.71 (1.16–2.51)	0.69 (0.49–0.99)
ACGV < 10th centile	20 (57.1)	60.61 (42.14–77.09)	61.38 (54.04–68.35)	21.51 (16.47–27.56)	89.92 (85.20–93.26)	1.57 (1.13–2.18)	0.64 (0.41–0.99)
EFW < 3rd centile or CPR < 5th centile or ACGV < 10th centile	27 (77.1)	82.35 (65.47–93.24)	46.35 (39.15–53.68)	21.37 (18.15–25.00)	93.68 (87.60–96.89)	1.54 (1.25–1.88)	0.38 (0.18–0.80)
CAO-2	71 (30.2)						
EFW < 3rd centile or CPR < 5th centile	27 (38.0)	41.43 (29.77–53.83)	70.19 (62.48–77.13)	37.66 (29.53–46.55)	73.38 (68.84–77.47)	1.39 (0.96–2.00)	0.83 (0.67–1.04)
ACGV < 10th centile	36 (50.7)	53.73 (41.12–66.00)	63.23 (55.12–70.82)	38.71 (31.80–46.10)	75.97 (70.40–80.78)	1.46 (1.08–1.98)	0.73 (0.55–0.97)
EFW < 3rd centile or CPR < 5th centile or ACGV < 10th centile	46 (64.8)	70.59 (58.29–81.02)	47.47 (39.48–55.55)	36.64 (31.84–41.72)	78.95 (71.48–84.88)	1.34 (1.09–1.66)	0.62 (0.41–0.93)

CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death. LR+/−, positive/negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 6 Area under the receiver–operating characteristics curve (AUC) and sensitivity at 50% and 90% specificity of three logistic regression models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as continuous variables, for the prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses

	CAO-1			CAO-2		
		Sensitivity (%) (95% CI) at:			*Sensitivity (%) (95% CI) at:*	
Model	*AUC (95% CI)*	*50% specificity*	*90% specificity*	*AUC (95% CI)*	*50% specificity*	*90% specificity*
EFW + CPR	0.669 (0.604–0.729)*	71.43 (53.7–85.4)	31.43 (16.9–49.3)	0.646 (0.580–0.707)†	68.57 (56.4–79.1)	25.71 (16.0–37.6)
ACGV	0.692 (0.627–0.752)	75.76 (57.7–88.9)	42.42 (25.5–60.8)	0.644 (0.577–0.707)	70.15 (57.7–80.7)	29.85 (19.3–42.3)
EFW + CPR + ACGV	0.741 (0.677–0.798)*	78.79 (61.1–91.0)	42.42 (25.5–60.8)	0.700 (0.633–0.759)†	75.76 (63.6–85.5)	37.88 (26.2–50.7)

*AUC for EFW + CPR *vs* AUC for EFW + CPR + ACGV: $P = 0.11$. †AUC for EFW + CPR *vs* AUC for EFW + CPR + ACGV: $P = 0.15$. CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death.

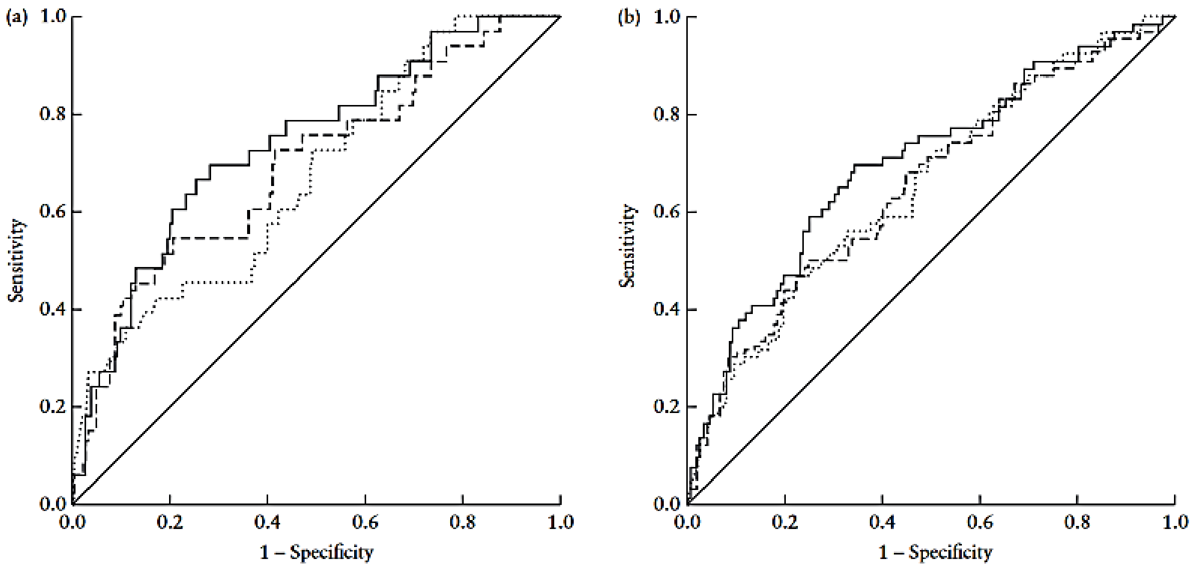

Figure 1 Receiver–operating characteristics curves of three logistic regression models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as continuous variables, for prediction of composite adverse outcomes 1 (a) and 2 (b) in near-term small-for-gestational-age fetuses. Composite adverse outcome 1 defined in accordance with definition used in POP study[12] as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. Composite adverse outcome 2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery (instrumental vaginal delivery or emergency Cesarean section for fetal distress) and perinatal death. ——, EFW + CPR + ACGV; – – –, ACGV; ⋯⋯, EFW + CPR.

Discussion

In this paper we demonstrate that in near-term fetuses diagnosed antenatally as SGA, a reduction (< 10th centile) in ACGV between 20 and 36 weeks is a risk factor for adverse outcome that is independent of EFW and CPR. The increase in the AUC when ACGV is added to the model is nevertheless not statistically significant.

Our findings suggest, but do not prove, that using ACGV in addition to EFW and CPR will improve risk stratification of near-term SGA fetuses. The detection of SGA has been a traditional cornerstone of antenatal care. The DIGITAT study [69] and a subsequent Cochrane review [70] concluded that there is no difference in terms of perinatal outcome between systematic induction of delivery at term vs expectant management in SGA fetuses, although the studies were underpowered for stillbirth.

Many guidelines consequently recommend expedited delivery from 37 or 38 weeks in pregnancies in which the EFW is < 10th centile irrespective of Doppler indices or the absence of pregnancy complications [87]. The limitations of this practice are increasingly appreciated. As SGA is just one manifestation of FGR, even the universal detection of SGA will have limited effects on stillbirth and neonatal morbidity [62,105].

As some SGA fetuses are constitutionally small [106], and probably not at increased perinatal risk, iatrogenic delivery maybe harmful [47]. It is therefore important to identify other predictors of adverse outcome. The most studied predictor is the CPR, which predicts adverse neonatal outcome in both SGA and AGA fetuses [97,107-109], although this is dependent on the interval between measurement and delivery [110]. EFW < 3rd centile [61], uterine artery Doppler [111,112] and biochemical markers such as placental growth factor [113] have also been used.

Algorithms for the prediction of adverse outcome in fetuses diagnosed as SGA near term have been proposed [75,79]. An adaptation of these that includes pregnancy-induced hypertension improves neonatal morbidity in SGA fetuses [47], demonstrating the need for better risk stratification. In addition, fetal growth velocity appears to play an important role. Both SGA and AGA fetuses with slow velocity have higher risks of preterm birth and longer neonatal unit admissions than those with normal growth [57].

Sovio et al. [39] used the difference between Z-scores of abdominal circumference (AC) measurements at 20 weeks and the third trimester in unselected nulliparous women, with non-revealed results. The lowest decile of ACGV detected the fetuses at highest risk of adverse outcome. Indeed if growth velocity was normal, an EFW <10th centile was not significantly associated with adverse neonatal outcome. Khalil et al. [97] demonstrated that a low CPR is indeed associated with reduced growth velocity, in both AGA and SGA fetuses. Among fetuses that were SGA and had a low CPR, 31% had an ACGV < 10th centile, whereas the figure was 16.1% when the CPR was normal. Nevertheless, 7.9% of AGA fetuses also had a low ACGV, suggesting that most fetuses with a low ACGV were neither SGA nor had a low CPR.

Caradeux et al. [114] analysed growth velocity of the EFW, as opposed to AC, in 472 SGA fetuses in the third trimester and found that fetuses with the lowest growth velocity were at slightly increased risk; however, this risk factor did not predict adverse outcomes better than existing models using EFW, CPR and uterine artery Doppler. In accordance with Khalil et al. [97], we found a significant correlation between ACGV and CPR, as well as EFW. We demonstrated that the growth velocity of the AC, determined from 20 weeks, is nevertheless an independent risk factor and, at least in fetuses thought to be SGA, using ACGV in addition to EFW < 3rd and CPR <5th centile might improve the prediction of adverse outcome in SGA fetuses.

Whilst the specificity of our method is poor (Tables 5 and 6), in this high risk group of fetuses, sensitivity is more important than specificity, as routine delivery is the usual default [87], and up to 50% of SGA fetuses are considered to show FGR [40]. This approximates to the specificities of the combination of all risk factors as binary variables.

We acknowledge some limitations of this study. Data on undiagnosed SGA fetuses were not available, sample size was small and the confidence intervals overlapped meaning that although ACGV is an independent risk factor, we cannot be confident that it improves screening performance. In addition, the outcomes explored were subject to other antepartum and intrapartum factors and to intervention, and therefore there is a potential 'treatment paradox'. The ACGV calculation uses only two points and its usage is limited by difficulties in quantification because of the complex methodology required for its calculation, a problem that is surmountable using automated software.

Finally, we did not collect data on third-trimester uterine artery, a tool that might add further sensitivity for risk stratification of SGA fetuses [75]. We did not consider fetuses that were not SGA. Whilst both ACGV [39] and CPR [95] may be important in AGA fetuses, it is likely that the screening performance in this group, even when using all our risk factors, is still poor. AGA fetuses account for more stillbirths than SGA ones, and it is in this group that specificity matters so that over-intervention is prevented. Ultimately, adverse perinatal events will be best predicted by modelling all independent risk factors as continuous variables.

In conclusion, estimation of fetal weight in the third trimester is an inadequate screening test for adverse perinatal outcome. Expediting delivery of all small fetuses, an increasing and widely recommended practice, should be restricted to those with risk factors. Our data suggest that a reference range of ACGV from 20 weeks should be incorporated in risk stratification.

Clinical phenotypes for risk stratification in small-for-gestational age fetuses

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Introduction

Small-for-gestational age (SGA) is usually defined as a significant deviation of ultrasound-estimated fetal weight or abdominal circumference from a population-based reference, with the typical threshold set at the 10th percentile [44]. SGA is associated with increased perinatal morbidity and mortality [54], suboptimal cardiovascular and neurological development [115] and long-term health problems [116-118]. Although identification of SGA fetuses is associated with a reduction in adverse perinatal outcome [118], a key aspect of clinical management is the ability to identify SGA fetuses at higher risk of adverse outcome.

Growth restriction is a complex condition with multiple etiological factors that determine its risk and consequences. After excluding cases of SGA associated with chromosomal abnormality, structural abnormality or infection [119], Doppler assessment of placental function and fetal wellbeing forms the basis for identifying intrauterine growth restriction (IUGR) in current clinical protocols [44,120]. Fetuses without abnormal SGA or IUGR are presumed to be constitutionally SGA. Although SGA fetuses with Doppler alterations have a worse perinatal outcome [39], constitutionally SGA fetuses also have a higher risk of poor perinatal and long-term outcomes when compared with appropriate-for-gestational-age (AGA) fetuses [60]. Thus, it is necessary to search for new strategies to identify better high-risk SGA patients.

Fetal growth can be affected by various pathological conditions during gestation, with obvious clinical manifestations. To promote more targeted interventions, we propose phenotypic sub-classification of SGA fetuses based on not only Doppler parameters, but also easily obtainable clinical information. The aim of this study was to evaluate whether clinical phenotypes of SGA fetuses can be identified and used to aid in risk stratification.

Methods

This was a multicentre observational cohort study conducted in two Spanish tertiary care university hospitals: Hospital Clınico Universitario Lozano Blesa in Zaragoza, Spain and Hospital Universitario Virgen de la Arrixaca in Murcia, Spain. A total of 17 631 consecutive singleton pregnancies were enrolled prospectively. SGA was defined as birth weight < 10th percentile according to INTERGROWTH-21st standards [27]. In all cases, gestational age was defined according to fetal crown–rump length on first-trimester ultrasound at 11–13weeks' gestation [121]. Data on maternal clinical and demographic characteristics as well as perinatal outcome were obtained from medical records. The ethics committee approved the protocol for this study.

Both centres used similar clinical protocols, which included a routine ultrasound scan between 32 and 37 weeks of gestation. Ultrasound recordings were performed by experienced operators (D.O., C.P., S.R.-M., J.L.D and C.d.P.). Fetuses with estimated fetal weight < 10th percentile according to local standards [122] were considered and consequently managed as suspected SGA during pregnancy. Patients were always managed by senior obstetricians, according to standard protocols for each clinical condition.

Following a previously published conceptual framework for developing a clinical phenotypic classification for preterm birth [123], SGA was classified according to maternal, fetal and placental conditions associated causally with SGA (Table 1).

Table 1 Definitions of maternal, fetal and placental conditions used for classification of small-for-gestational-age fetuses

Condition	*Description*
Maternal	
Hypertension disorder[33]	Blood pressure > 140/90 mmHg; including: pregnancy-induced hypertension, chronic hypertension prior to pregnancy, pre-eclampsia, eclampsia and HELLP syndrome
Chronic maternal disease	Autoimmune diseases, maternal chronic disease, diabetes mellitus or chronic infection (e.g. human immunodeficiency virus, hepatitis B virus)
Gestational diabetes[34]	Oral glucose tolerance test with two elevated values, with or without insulin (four time-interval normal values: 105, 190, 165 and 145 mg/dL at baseline)
Use of ART[35]	Artificial insemination, *in-vitro* fertilization, with or without egg donation
Fetal	
Congenital anomaly	Chromosomal anomaly, morphological alteration or intrauterine infection
Intrauterine growth restriction[16]	Birth weight < 3^{rd} percentile; birth weight < 10^{th} percentile and Doppler alterations (UA-PI > 95^{th} percentile, MCA-PI < 5^{th} percentile, CPR < 5^{th} percentile or mean UtA-PI > 95^{th} percentile)[36]
Preterm birth	Spontaneous delivery before 37 weeks' gestation
Placental	
Second- or third-trimester bleeding	Placenta previa, placenta accreta or placental abruption

ART, assisted reproduction techniques; CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

After a comprehensive descriptive analysis following a hierarchical, agglomerative approach combining individual cases into clusters as different from one another as possible, a nine-cluster model provided a categorization of SGA clinical phenotypes highly consistent with our a-priori conceptual classification. Therefore, every SGA fetus in this study was grouped into four clusters according to maternal condition (hypertension/pre-eclampsia (PE), gestational diabetes, another chronic maternal disease and use of assisted reproduction techniques), three clusters according to fetal condition (congenital anomaly, IUGR and preterm birth) and one cluster according to placental condition (second- or third-trimester haemorrhage).

IUGR was defined according to The International Society of Ultrasound in Obstetrics and Gynecology definition [124]. The remaining SGA fetuses without associated clinical manifestation were grouped into another cluster (none).

Statistical analysis was performed using SPSS Statistics v19 (IBM Corp., Armonk, NY, USA). Because many fetuses exhibited more than one maternal, fetal or placental condition, a two-step cluster algorithm was used [125,126]. In step one, perinatal mortality rates for each of the nine clusters were analysed, with cases classified initially into more than one cluster, if appropriate. In step two, cases that were included initially in more than one group were reclassified and assigned to only one cluster that was associated with the highest mortality risk.

Thus, in the final analysis, every patient was placed in a single cluster. Preterm cases that were also included in another cluster were not assigned to the prematurity cluster because preterm birth was indicated medically in most cases. To evaluate the independence of each cluster as a clinical entity, perinatal mortality and neonatal intensive care unit (NICU) admission rates were calculated.

Delivery and perinatal outcomes were compared using chi-square test among SGA clusters, and the associations between outcomes and each cluster were evaluated by calculating odds ratios (OR), adjusted for gestational age.

Results

Of the 17 631 consecutive singleton pregnancies included in this study, 1274 (7.2%) were defined as SGA. There were differences in baseline demographic characteristics as well as evolution of the pregnancy between SGA and non-SGA groups. As expected, the overall SGA cohort had a worse perinatal outcome, with an approximately three-times higher rate of perinatal mortality per 1000 cases compared with the AGA cohort (14.13 vs 4.16; P<0.001) (Table 2).

Table 2 Maternal demographic characteristics and perinatal outcome of small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) cohorts

Characteristic/outcome	*AGA (n = 16 357)*	*SGA (n = 1274)*	P
Maternal age (years)	31.7 ± 5.7	31.5 ± 5.9	0.244
Maternal BMI (kg/m^2)	25.0 ± 4.8	24.0 ± 4.6	< 0.001
Caucasian	15 634 (95.6)	1222 (95.9)	0.570
Smoker	2162 (13.6)	335 (27.1)	< 0.001
Nulliparous	8252 (50.4)	827 (64.9)	< 0.001
Previous CS	286 (1.7)	17 (1.3)	0.273
ART use	575 (3.5)	56 (4.4)	0.103
GA at delivery (days)	276.8 ± 16.3	270.4 ± 21.1	< 0.001
Preterm birth	1027 (6.3)	182 (14.3)	< 0.001
Hypertension/PE	283 (1.7)	66 (5.2)	< 0.001
Gestational diabetes	422 (2.6)	21 (1.6)	0.041
Female fetus	8493 (52)	639 (50.2)	0.226
Fetal anomaly	149 (0.9)	13 (1.0)	0.693
Elective delivery*	5655 (34.6)	623 (49.3)	< 0.001
Instrumental delivery	2894 (17.7)	192 (15.1)	< 0.001
CS	3649 (22.3)	387 (30.4)	< 0.001
CS for fetal acidosis†	679 (4.2)	154 (12.1)	< 0.001
5-min Apgar score < 7	168 (1.0)	46 (3.7)	< 0.001
NICU admission	1011 (6.2)	246 (19.3)	<0.001
Stillbirth	63 (0.4)	15 (1.2)	< 0.001
Perinatal mortality	68 (0.4)	18 (1.4)	< 0.001
Perinatal mortality rate (per 1000 cases)	4.16	14.13	

Data are given as mean ± SD or *n* (%), unless indicated otherwise. Continuous variables were compared using *t*-test, while categorical variables were compared using chi-square test. *Labor induction or elective Cesarean section (CS). †Umbilical artery pH < 7.10. ART, assisted reproduction techniques; BMI, body mass index; GA, gestational age; NICU, neonatal intensive care unit; PE, pre-eclampsia.

Fetuses that were included initially in more than one group were reclassified and assigned to only one of their clusters with the highest mortality risk (based on step one of the cluster analysis) (Table S1).

Table S1 Perinatal mortality of each step-one cluster

Clinical cluster	**Perinatal mortality, *n* (%)**
Preterm	18 (9.9)
Second- or third-trimester bleeding	1 (8.3)
Congenital anomalies	1 (7.7)
Gestational diabetes	1 (4)
IUGR	16 (3.6)
Chronic maternal disease	1 (2.4)
Hypertension/pre-eclampsia	1 (1.5)
None	1 (0.1)
Assisted reproduction techniques	0

Some cases are included in more than one cluster. IUGR, intrauterine growth restriction.

Table 3 summarizes the distribution of SGA fetuses across the final nine clusters. Of note, the following two clusters encompassed more than 85% of all cases: the “none” cluster (54.1%) and “IUGR” [124] cluster (33.2%). The remaining SGA cases were distributed evenly across the other seven clusters.

Table 3 Nine clinical phenotypes of 1274 small-for-gestational-age fetuses according to maternal, fetal or placental condition

Cluster	*Main condition*	n *(%)*
1	None	689 (54.1)
2	Intrauterine growth restriction	423 (33.2)
3	Preterm birth	31 (2.4)
4	Hypertension/pre-eclampsia	27 (2.1)
5	Assisted reproduction techniques	28 (2.2)
6	Chronic maternal disease	26 (2.0)
7	Gestational diabetes	26 (2.0)
8	Congenital anomaly	12 (0.9)
9	Second- or third-trimester bleeding	12 (0.9)

After reclassifying each case into a single clinical cluster, all delivery and perinatal outcomes were significantly different among clusters (Table S2, Figures 1–3).

Table S2 Perinatal outcome of small-for-gestational-age fetuses, according to clinical phenotype

Outcome	Total, n (%)	None, n (%)	Intrauterine growth restriction, n (%)	Preterm birth, n (%)	Hypertension/ preeclampsia, n (%)	Assisted reproduction techniques, n (%)	Maternal chronic pathologies, n (%)	Gestational diabetes, n (%)	Congenital anomalies, n (%)	Second / third trimester haemorrhage, n (%)	P value
Caesarean section	387 (30.4)	156 (22.6)	160 (37.8)	9 (29)	20 (71.4)	6 (21.4)	9 (34.6)	11 (42.3)	7 (58.3)	11 (91.7)	<0.001
Caesarean section fetal acidosis	154 (12.1)	67 (9.8)	62 (14.8)	5 (16.1)	4 (14.3)	3 (10.7)	1 (3.8)	4 (15.4)	2 (16.7)	6 (50)	<0.001
Elective delivery	623 (48.9)	305 (44.3)	226 (54.3)	10 (32.2)	20 (74.1)	19 (67.9)	11 (42.3)	23 (88.5)	7 (63.7)	3 (27.3)	<0.001
5-min Apgar score < 7	46 (3.6)	8 (1.2)	27 (6.6)	4 (13.3)	3 (11.1)	0	0	0	2 (18.2)	2 (18.2)	<0.001
NICU admission	246 (19.3)	35 (5.1)	153 (36.2)	16 (51.6)	17 (60.7)	2 (7.1)	5 (19.2)	4 (15.4)	7 (58.3)	8 (66.7)	<0.001
Stillbirth	15 (1.2)	1 (0.1)	12 (2.8)	0	0	0	0	0	1 (8.3)	1 (8.3)	<0.001
Perinatal mortality	18 (1.4)	1 (0.1)	13 (3.1)	1 (3.2)	0	0	0	1 (3.8)	1 (8.3)	1 (8.3)	<0.001

NICU, neonatal intensive care unit

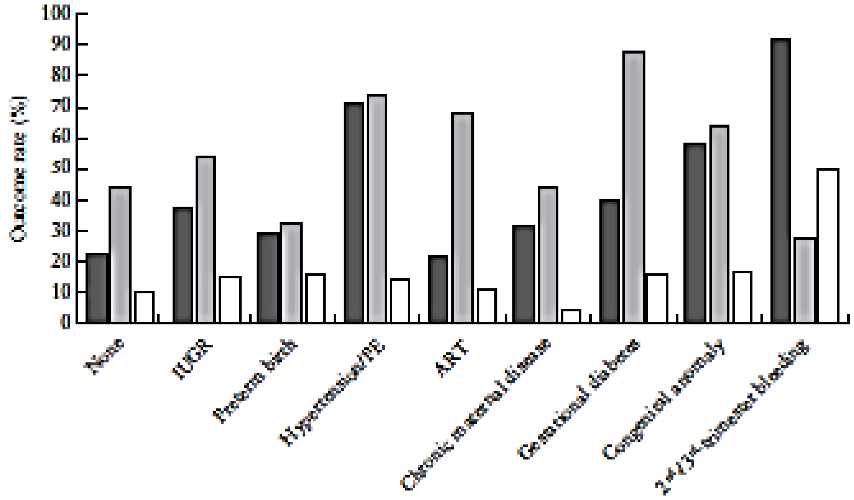

Figure 1 Rates of delivery type according to small-for-gestational-age clinical phenotype in 1274 fetuses. There was a significant difference in the rate of each type of delivery across the nine clusters ($P < 0.001$). ■, Cesarean section; □, elective delivery; □, Cesarean section for fetal acidosis. ART, assisted reproduction techniques; IUGR, intrauterine growth restriction; None, small-for-gestational-age fetuses with no associated clinical abnormality; PE, pre-eclampsia.

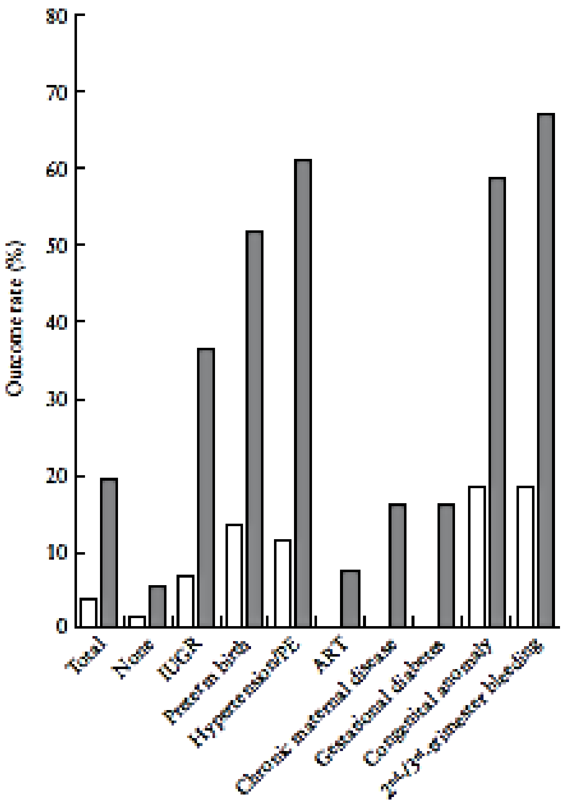

Figure 2 Rates of neonatal intensive care unit admission (■) and 5-min Apgar score < 7 (□) according to small-for-gestational-age clinical phenotype in 1274 fetuses. There was a significant difference in the rate of each outcome across the nine clusters ($P < 0.001$). ART, assisted reproduction techniques; IUGR, intrauterine growth restriction; None, small-for-gestational-age fetuses with no associated clinical abnormality; PE, pre-eclampsia.

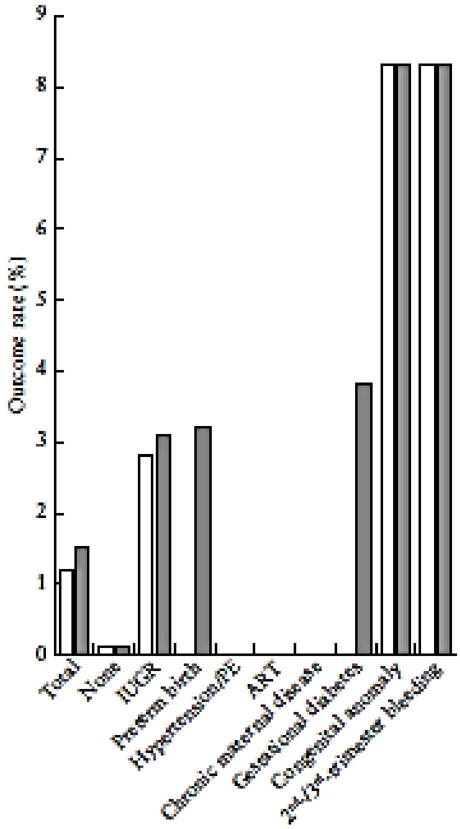

Figure 3 Rates of stillbirth (□) and perinatal mortality (■) according to small-for-gestational-age clinical phenotype in 1274 fetuses. There was a significant difference in the rate of each outcome across the nine clusters ($P < 0.001$). ART, assisted reproduction techniques; IUGR, intrauterine growth restriction; None, small-for-gestational-age fetuses with no associated clinical abnormality; PE, pre-eclampsia.

We also calculated the ORs to evaluate the association of delivery and perinatal outcome with each SGA clinical phenotype compared with non-SGA fetuses, adjusted for gestational age (Table 4).

Table 4. Odds ratios for perinatal outcomes of each small-for-gestational-age clinical phenotype compared with appropriate-for-gestational-age fetuses, adjusted for gestational age

Outcome	*None*	*IUGR*	*Preterm birth*	*Hypertension/PE*	*ART*	*Chronic maternal disease*	*Gestational diabetes*	*Congenital anomaly*	*Second-/third-trimester bleeding*
CS	1.05 (0.87–1.26)	1.65 (1.34–2.03)	0.78 (0.35–1.73)	5.20 (2.24–12.07)	1.00 (0.403–2.467)	1.62 (0.71–3.68)	2.39 (1.086–5.249)	3.56 (1.11–11.37)	19.59 (2.47–155.50)
CS for fetal acidosis	2.52 (1.93–3.28)	3.71 (2.79–4.92)	3.68 (1.40–9.69)	3.42 (1.17–9.98)	2.80 (0.84–9.31)	0.88 (0.119–6.52)	4.08 (1.40–11.90)	4.15 (0.91–19.01)	17.98 (5.71–56.60)
Elective delivery	1.50 (1.28–1.75)	2.21 (1.82–2.70)	0.87 (0.41–1.85)	6.11 (2.45–15.26)	4.00 (1.807–8.838)	1.37 (0.63–2.99)	14.40 (4.32–48.97)	3.24 (0.95–11.08)	0.68 (0.18–2.55)
5-min Apgar score < 7	1.35 (0.66–2.76)	3.53 (2.21–5.64)	5.25 (1.67–16.51)	5.13 (1.43–18.35)	N/A	N/A	N/A	14.05 (2.91–67.85)	5.38 (1.03–28.04)
NICU admission	1.00 (0.71–1.43)	5.32 (4.18–6.78)	4.08 (1.91–8.72)	7.31 (3.12–17.17)	1.48 (0.34–6.33)	2.47 (0.80–7.65)	2.33 (0.71–7.63)	10.65 (3.07–36.97)	5.19 (1.14–23.72)
Stillbirth	0.43 (0.06–3.14)	6.02 (3.19–11.35)	N/A	N/A	N/A	N/A	N/A	18.71 (2.36–148.29)	11.16 (1.39–89.70)
Perinatal mortality	0.41 (0.06–2.94)	5.93 (3.21–10.95)	4.65 (0.62–35.01)	N/A	N/A	N/A	9.59 (1.27–72.57)	17.17 (2.17–136.12)	9.94 (1.23–80.02)

Values in parentheses are 95% CI. ART, assisted reproduction techniques; CS, Cesarean section; IUGR, intrauterine growth restriction; N/A, not applicable; NICU, neonatal intensive care unit; PE, pre-eclampsia.

The rate of caesarean section was highest in the second- or third-trimester haemorrhage cluster (91.7%; OR, 19.59 (95% CI, 2.47–155.50)) and hypertension/PE cluster (71.4%; OR, 5.20 (95% CI, 2.24–12.07)). Conversely, the rate of caesarean section was similar between SGA and non-SGA fetuses in assisted-reproduction-technique, preterm-birth, maternal-chronic-pathology and none clusters.

Of note, the rate of caesarean section for fetal acidosis was 50% in the second- or third-trimester-haemorrhage cluster (OR, 17.98 (95% CI, 5.71–56.60)); this was much higher than the rates for other clusters, which ranged from 9.8% to 16.7%.

The gestational diabetes cluster (88.5%; OR, 14.40 (95% CI, 4.32–48.97)) and hypertension/PE cluster (74.1%; OR, 6.11 (95% CI, 2.45–15.26)) had the highest rate of elective delivery.

Regarding perinatal outcome, the clusters of second or third-trimester haemorrhage and congenital anomaly had the worst outcome, with NICU admission rates of 66.7% (OR, 5.19 (95% CI, 1.14–23.72)) and 58.3% (OR, 10.65 (95% CI, 3.07–36.97)), respectively, and rates of 5-min Apgar score < 7 of 18.2% (OR, 5.38 (95% CI, 1.03–28.04)) and 18.2% (OR, 14.05 (95% CI, 2.91–67.85)), respectively.

The hypertension/PE, preterm-birth and IUGR phenotypes were also associated with an increased risk of poor perinatal outcome, with NICU admission rates of 60.7% (OR, 7.31 (95% CI, 3.12–17.17)), 51.6% (OR, 4.08 (95% CI, 1.91–8.72)) and 36.2% (OR, 5.32 (95% CI, 4.18–6.78)), respectively.

We also calculated the added risk of being SGA or non-SGA for each clinical condition, adjusted for gestational age (Table S3). For example, pregnancies with gestational diabetes and a SGA fetus had a significantly higher risk of perinatal mortality compared to those with gestational diabetes and an AGA fetus (OR, 24.40 (95% CI, 1.31–453.91)).

Table S3 Perinatal outcome of each small-for-gestational-age clinical phenotype compared with appropriate for gestational age fetuses with the same clinical condition, adjusted for gestational age

Outcome	None, OR (95% CI)	Preterm birth, OR (95% CI)	Hypertension/ Pre-eclampsia, OR (95% CI)	Assisted reproduction techniques, OR (95% CI)	Maternal chronic pathologies, OR (95% CI)	Gestational diabetes, OR (95% CI)	Congenital anomalies, OR (95% CI)	Second- or third-trimester haemorrhage, OR (95% CI)
Cesarean section	1.18 (0.98-1.42)	1.02 (0.46-2.26)	1.27 (0.49-3.33)	0.55 (0.22-1.38)	1.11 (0.47-2.59)	1.29 (0.58-3.00)	1.90 (0.55-6.50)	1.54 (0.18-13.09)
Cesarean section for fetal acidosis	2.98 (2.28-3.90)	4.12 (1.49-11.42)	1.02 (0.31-3.40)	2.30 (0.64-8.30)	0.53 (0.07-4.03)	2.71 (0.87-8.48)	3.96 (0.69-22.65)	1.93 (0.52-7.09)
Elective delivery	1.81 (1.55-2.11)	0.99 (0.46-2.15)	0.67 (0.24-1.90)	2.26 (1.00-5.11)	0.71 (0.33-1.52)	2.27 (0.66-7.74)	1.86 (0.52-6.68)	0.57 (0.12-2.60)
5-min Apgar score < 7	2.16 (1.32-4.50)	2.40 (0.80-7.20)	0.58 (0.11-3.15)	NA	NA	NA	7.43 (0.78-71.08)	0.40 (0.06-2.81)
NICU admission	1.49 (1.04-2.12)	1.94 (0.94-3.99)	1.71 (0.54-5.39)	2.51 (0.51-12.26)	1.45 (0.38-5.48)	2.41 (0.78-7.47)	1.24 (0.35-4.39)	2.43 (0.57-10.50)
Stillbirth	0.84 (0.11-6.30)	NA	NA	NA	NA	NA	3.70 (0.33-41.30)	0.67 (0.07-6.47)
Perinatal mortality	0.84 (0.11-6.30)	0.89 (0.12-6.77)	NA	NA	NA	24.40 (1.31-453.91)	3.70 (0.33-41.30)	0.67 (0.07-6.47)

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit; OR, odds ratio.

Finally, we classified our SGA fetuses into three patterns of stillbirth or perinatal mortality risk (Table 4 and Figure 3). With regard to perinatal mortality, the highest risk was associated with congenital anomaly (8.3%; OR, 17.17 (95% CI, 2.17–136.12)) and second- or third-trimester haemorrhage (8.3%; OR, 9.94 (95% CI, 1.23–80.02)); the medium risk was associated with gestational diabetes (3.8%; OR, 9.59 (95% CI, 1.27–72.57)), preterm birth (3.2%; OR, 4.65 (95%CI, 0.62–35.01)) and IUGR (3.1%; OR, 5.93 (95%CI, 3.21–10.95)); and the lowest risk was associated with the remaining clusters (none, hypertension/PE, assisted reproduction technique and maternal chronic pathology).

It is noteworthy that we found no difference in perinatal mortality rates between the "none" cluster (54.1% of the SGA group) and the non-SGA cohort (0.1% vs 0.4%; OR, 0.41 (95%CI, 0.06–2.94); P=0.27).

Discussion

In this study, we identified nine SGA clinical phenotypes associated with significantly different patterns of risk for adverse perinatal outcome. Accordingly, we proposed a practical sub-classification system of SGA fetuses based on Doppler parameters as well as easily obtainable clinical information to open new research pathways for developing more targeted interventions.

Doppler assessment is undeniably important for managing SGA fetuses, as it is the main tool, together with estimated fetal weight, for diagnosing and monitoring fetuses with IUGR [127]. The understanding of etiological complexities of IUGR remains inadequate, but is required for the development of better preventive and treatment measures.

As the role of angiogenic markers in managing SGA is yet to be established completely [128-130], fetal monitoring for SGA continues to focus on ultrasound and Doppler findings [124] which serve as the main tool for risk stratification [39,131]. Our findings support this concept: based on previously established criteria [119], 33.2% of SGA fetuses in this study were classified as IUGR [124], and 13/18 (72.2%) perinatal deaths in our cohort occurred in this group. However, according to current classification systems [44,119], the group of SGA fetuses without Doppler alterations or congenital anomaly continues to have worse perinatal and long-term outcomes compared with AGA fetuses [60].

Interventions for SGA have had limited benefit because they tend to improve outcome only in specific subsets of cases. As healthcare evolves from reactive care to more cost-effective predictive, preventive and personalized care (treating the cause rather than symptoms of a disease) [132], intensive research activity has focused on placental biomarkers for phenotypic characterization and risk stratification of fetal smallness [133,134]. Despite important advances in research on the biological basis of IUGR [135-137], the currently available information is complex and has not yet been translated into clinical practice.

Some authors have suggested that we can improve characterization and phenotyping of pathologies, such as preterm birth [123] and IUGR [138], based on maternal, fetal and placental clinical conditions. Accordingly, 12 preterm-birth phenotypes associated with differing neonatal outcome [125] and neurodevelopmental outcome up to 2 years of age [139] were identified recently. Following this pragmatic conceptual framework and using easily obtainable clinical information, in addition to commonly accepted SGA clinical phenotypes (IUGR, constitutional SGA and congenital anomaly), we identified six clinical phenotypes (preterm birth, hypertension/PE, assisted reproduction technique, chronic maternal disease, gestational diabetes and second or third-trimester bleeding), which encompassed 11.8% of all SGA fetuses and were associated with a significantly increased risk of adverse perinatal outcome.

These fetuses, which would have been considered low-risk SGA according to current classification systems, accounted for three of four perinatal deaths outside the IUGR and congenital anomaly clusters (i.e. fetuses without specific pathology detected on Doppler and ultrasound assessments).When excluding these fetuses, the remaining 54.1% of SGA fetuses without other clinical conditions (i.e. the none cluster) had similar risk of 5-min Apgar score < 7, NICU admission, stillbirth and perinatal mortality, when compared with non-SGA fetuses.

Focusing on clinical management of SGA, three practical conclusions can be derived from our findings. First, according to international consensus, SGA fetuses without congenital anomaly and with normal Doppler findings should be monitored closely, with delivery near term [69,120]. However, when considering other clinical conditions in addition to abnormality on Doppler or ultrasound, we identified a small group of fetuses (11.8%) with a significantly worse perinatal outcome compared with AGA fetuses. Second, exclusion of the SGA fetuses with other clinical conditions reduced considerably the perinatal risk of the remaining SGA fetuses. Third, it is important to highlight the increased risk when SGA is accompanied by other obstetric pathologies, including the significantly increased perinatal mortality in pregnancies with a SGA fetus and gestational diabetes, compared to those with an AGA fetus and gestational diabetes (OR, 24.40).

Our data do not allow specific clinical management recommendations, but emphasize the need to include the identified clinical variables both in routine clinical practice and in future studies to improve identification of SGA fetuses requiring intervention.

This study has some limitations. Each patient in our cohort was included in only one cluster, although the same fetus may have exhibited several concomitant clinical conditions. Nevertheless, we opted for a two-step cluster analysis to simplify the analysis and potential clinical management. Including each fetus in its highest risk cluster is consistent with the usual and practical reasoning employed in clinical management. Our analysis generated distinct, clinically reasonable clusters with different mortality and morbidity rates, supporting its usefulness in classifying our study population. Another limitation was that the sample size was insufficient for adequate statistical power when analysing infrequent perinatal outcomes. However, despite the wide 95%CIs, we found significant differences in variables with major clinical relevance. Unfortunately, we do not have data regarding medium- and long-term infant development.

Despite these drawbacks, this study meets the main goal of generating hypotheses. Larger clinical studies are necessary to develop specific guidelines for action and to establish etiological phenotypes.

In conclusion, we identified nine SGA clinical phenotypes associated with different patterns of perinatal outcome. Our findings suggest that considering clinical characteristics in addition to ultrasound examination findings may improve risk stratification and decision-making for management of SGA fetuses.

Future clinical trials investigating management of fetuses with SGA should take into account clinical information in addition to Doppler and fetal weight measures.

LGA cohort

Ultrasound predictors of adverse outcome in pregnancy complicated by pre-existing and gestational diabetes

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Introduction

Pre-existing diabetes mellitus (DM) and gestational diabetes (GDM) are associated with adverse pregnancy outcomes.[140] These include, particularly with DM, perinatal mortality and morbidity related to poor placental function [141], and to mechanical issues such as caesarean section (CS) or shoulder dystocia, in addition to long-term sequelae [140].

Prevention primarily involves (1) glycemic control and (2) optimization of the time and method of birth, balancing the increased risks of preterm or early term birth against the risks of mortality and morbidity [140].

The most established manifestation of poor placental function is being small for gestational age. Methods are established to determine those at most risk. Yet fetuses subject to hyperglycaemia, despite their increased risk, tend to be larger [142]. Hyperinsulinemia increases size and the effects of poor placental function are potentially masked [141].

Increased size appears to correlate with increased risk and is the only established ultrasound risk factor [53,140]. Regular ultrasound assessment of fetuses is recommended, but has moderate sensitivity and specificity for size, and poor predictive value for adverse outcomes [53,140]. The identification of which large fetuses of diabetic pregnancy are at most risk is even less clear. The American College of Obstetricians and Gynaecologists (2018) states only that fetal umbilical artery (UA) Doppler may be useful in monitoring babies with fetal growth restriction [140]. This means that for the majority of diabetic pregnancies, fetal Doppler, so crucial to timing birth in other at-risk pregnancies, has a little known role.

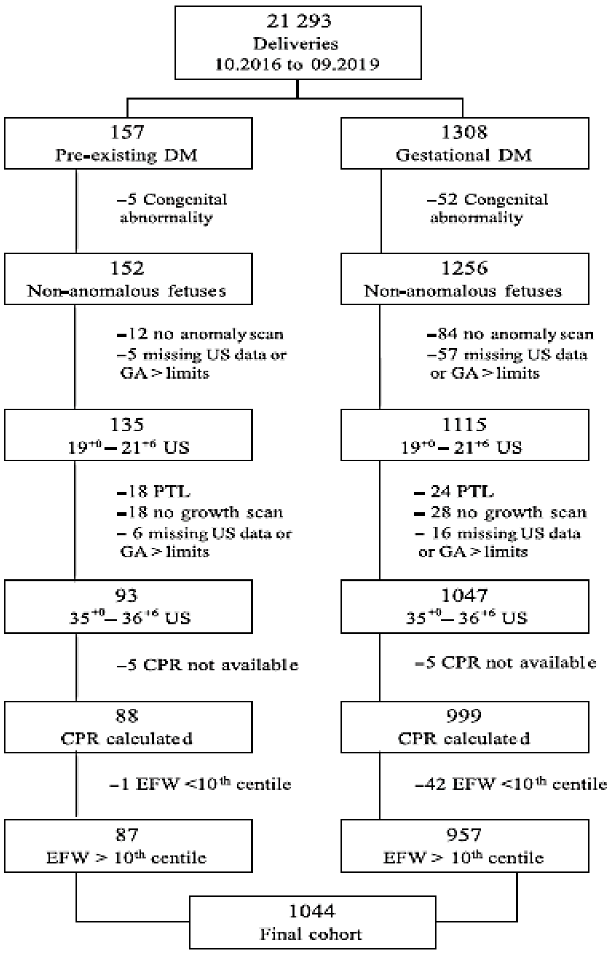
Recent analyses have examined ultrasound markers of placental function other than size. Fetal growth rate, as measured by the abdominal circumference growth velocity (ACGV), adds to the prediction of adverse outcomes in both small and large fetuses [57]. Equally, the ratio of Umb A to middle cerebral artery (MCA) pulsatility index (PI) (cerebroplacental ratio [CPR]) is a predictor of adverse outcomes in appropriate-for-gestational-age fetuses as well as in small-for-gestational-age ones [94].

The aim of this paper is to assess the role of ACGV and CPR as markers of placental function, in predicting adverse perinatal outcome in pregnancies with GDM or pre-existing DM.

Methods

This is a retrospective analysis of all women with singleton pregnancies and diagnosed with GDM or pre-existing DM, with an estimated delivery date between October 2016 and September 2019, who delivered from 35+0 completed weeks in a single large UK maternity unit. All except in vitro fertilization pregnancies were dated using crown-rump length before 14 weeks or by head circumference between 14+0 and 18+0 weeks. The selection of the cohort is shown in Figure 1.

FIGURE 1 Flow diagram of the cohort selection



All women underwent routine ultrasound with biometry between 18+0 and 21+6 weeks and a scan for fetal biometry, liquor volume assessment, and Umb A and MCA Doppler at 31+0–32+6 weeks and at 35+0–36+6 weeks. Pregnancies complicated by fetal abnormality or aneuploidy or those where a scan with full biometry had not also been performed were excluded. We also excluded fetuses with an estimated fetal weight (EFW) below the 10th centile because of their rarity and because, with GDM their management is largely irrespective of hyperglycaemia [124].

The diagnosis of GDM was made using screening of at-risk groups, according to National Institute for Health and Care Excellence criteria: body mass index greater than 30 kg/m2, previous macrosomic baby, previous gestational diabetes, family history of diabetes in a first-degree relative, or ethnicity with a high prevalence of diabetes [143].

A 75-g glucose tolerance test was administered between 24 and 30 weeks and, in addition, before 20 weeks in those with a history of GDM: hyperglycaemia was diagnosed according to International Association of Diabetes in Pregnancy Study Group criteria [144].

Ultrasound examinations were carried out by accredited sonographers using Voluson E6 and E8 ultrasound machines (GE Healthcare) with a 2-to 8-Hz convex probe. Measurements were recorded prospectively using archiving software

(Viewpoint, GE Healthcare) and transferred using DICOM. Doppler measurements were obtained according to International Society of Ultrasound in Obstetrics and Gynecology guidelines [21]. The EFW was calculated using Hadlock's 1985 equation [46].

Management was in a specialist clinic with multidisciplinary input from diabetologists, dieticians, obstetricians, and midwives. Glucose levels of those with GDM were monitored remotely using an app (GDm-Health; Sensynehealth.com) and dietary modification and exercise advice; also, if appropriate, oral metformin and subcutaneous insulin were used. Women with pre-existing diabetes were also monitored remotely. Target glucoses were less than 5.3 mmol/L (fasting) and less than 7.8 mmol/L (1 h postprandial).

Fetuses were defined as appropriate for gestational age when EFW was at the 10^{th} centile or above and less than the 90^{th} centile, and large for gestational age when EFW was at the 90^{th} centile or above, according to Hadlock et al.[46].

An ACGV above the 90^{th} centile was calculated according to Vannuccini et al. [103]. CPR was calculated as the ratio of the MCA PI to the Umb A PI and a CPR below the 5^{th} centile was defined according to Ciobanu et al. [145]. Polyhydramnios was defined as a deepest vertical pool of more than 8.0 cm [146].

Data were routinely collected prospectively and were merged according to a unique identifier from neonatal (Badgernet), maternity (Cerner), and ultrasound (Viewpoint, GE Healthcare) records.

The composite adverse outcome (CAO) was defined as the presence of at least one of perinatal death, arterial cord pH less than 7.1, admission to Neonatal Unit, 5-minute Apgar score less than 7, severe hypoglycaemia requiring treatment, or CS for suspected fetal compromise.

We considered the following ultrasound markers: EFW above or equal to the 90^{th} centile, polyhydramnios, ACGV above or equal to the 90^{th} centile and CPR below or equal to the 5^{th} centile. A chi-squared test, generating odds ratios (OR) with 95% confidence intervals (CI), was used to test their association with the CAO. Logistic regression was used to determine which ultrasound markers were independent risk factors. The OR for the CAO with different combination of ultrasound markers found to be independent predictors of CAO were calculated. The area under the curve (AUC) was calculated for these. Statistical analysis was performed with IBM SPSS Statistics, Version 26.0 (IBM). Ethical approval was granted on July 27, 2017 (IRAS project ID 222260; REC reference: 17/SC/0374).

Results

A total of 1044 pregnancies were included, comprising 87 pregnancies involving pre-existing diabetes, and 957 involving gestational diabetes.

A flow diagram of the cohort is shown in Figure 1. Of those women with GDM, 148 (15.5%) were diagnosed before 24 weeks, the rest after.

The CAO was present in 174 (16.7%) pregnancies. Nulliparity, lower gestational age at birth, preeclampsia and possibly Caucasian ethnicity were associated with an increased incidence (Table 1).

TABLE 1 Population characteristics as risk factors for composite adverse outcome in fetuses with an estimated fetal weight above the 10th centile

	All patients *n* = 1044 (100%)	CAO present *n* = 174 (16.7%)	CAO absent 870 (83.3)	*p* value
Maternal age (year), mean ± SD	32.4 ± 5.5	31.5 ± 5.3	32.6 ± 5.5	0.018
Body mass index (kg/m²), mean ± SD	30.4 ± 6.8	31.0 ± 7.1	30.2 ± 6.7	0.169
Body mass index ≥ 30 kg/m², *n*/*N* (%)	520/1038 (50.1)	93/173 (53.8)	427/865 (49.4)	0.291
Caucasian ethnicity, *n*/*N* (%)	519/719 (72.2)	71/110 (64.5)	448/609 (73.6)	0.052
Nulliparity, *n* (%)	413 (39.6)	100 (57.5)	313 (36.0)	<0.001
In vitro conception, *n* (%)	23 (2.2)	3 (1.7)	20 (2.3)	0.637
Hypertension, *n*/*N* (%)	65/720 (9.0)	11/109 (10.1)	54/611 (8.8)	0.674
Smoker, *n*/*N* (%)	100/1035 (9.7)	18/173 (10.4)	82/862 (9.5)	0.717
Pre-eclampsia, *n* (%)	68 (6.5)	21 (12.1)	47 (5.4)	0.001
Male fetuses, *n* (%)	562 (53.8)	99 (56.9)	463 (53.2)	0.374
Gestational age at delivery (days), mean ± SD	273.9 ± 8.6	271.0 ± 10.2	274.5 ± 8.1	<0.001
Birth at <37^{+0} weeks, *n* (%)	38 (3.6)	17 (9.8)	21 (2.4)	<0.001
Induction of labor, *n* (%)	481 (46.1)	85 (48.9)	396 (45.5)	0.421

Note: Continuous variables were compared using the Mann-Whitney *U* test for non-normally distributed independent samples. Categorical variables were compared using a chi-squared test. CAO: Composite adverse outcome: 1+ of perinatal death, arterial cord pH < 7.1, admission to neonatal unit, 5-minute Apgar <7, severe hypoglycemia requiring treatment, or CS for suspected fetal compromise.

Table 2 shows the association between the four ultrasound markers and the adverse outcome. In the entire cohort, EFW at the 90th centile or above, ACGV at the 90th centile or above, CPR at the 5th centile or below, but not polyhydramnios, were significantly associated with the CAO. Only EFW at the 90th centile or above and CPR at the 5th centile or below were independent risk factors. When sub-divided into pre-existing DM and GDM, no statistically significant associations were found.

TABLE 2 Association between the ultrasound markers and the incidence of composite adverse outcome

Appropriate for gestational age fetuses		CAO present			
	N (%)	*N* (%)		OR (95% CI)	AOR (95% CI)[a]
All hyperglycemic pregnancy					
Total	1044 (100)	174 (16.7)			
Risk factor		US RF present	US RF absent		
EFW ≥90th	135 (12.9)	34 (25.2)	101 (74.8)	1.85 (1.21–2.84)	1.66 (1.002–2.75)
ACGV ≥90th	167 (16.0)	37 (22.2)	130 (77.8)	1.54 (1.02–2.31)	1.21 (0.75–1.96)
CPR ≤5th	75 (7.2)	20 (26.7)	55 (73.3)	1.92 (1.21–3.30)	1.91 (1.11–3.30)
Polyhydramnios	52 (5.0)	12 (23.1)	40 (76.9)	1.53 (0.79–2.99)	–
GDM only					
Total	957 (100)	137 (14.3)			
Risk factor					
EFW ≥90th	106 (11.1)	19 (17.9)	87 (82.1)	1.357 (0.80–2.23)	–
ACGV ≥90th	137 (14.3)	20 (14.6)	117 (85.4)	1.027 (0.62–1.72)	–
CPR ≤5th	58 (6.1)	10 (17.2)	48 (82.8)	1.266 (0.63–2.57)	–
Polyhydramnios	44 (4.6)	9 (20.4)	35 (79.5)	1.625 (0.76–3.47)	–
Pre-existing DM only					
Risk factor	87 (100)	37 (42.5)			
EFW ≥ 90th	29 (33.3)	15 (51.7)	14 (48.3)	1.753 (0.71–4.32)	–
ACGV ≥ 90th	30 (34.5)	17 (56.7)	13 (43.3)	2.49 (0.98–5.96)	–
CPR ≤ 5th	17 (19.5)	10 (58.8)	7 (41.2)	2.28 (0.77–6.69)	–
Polyhydramnios	8 (9.2)	3 (37.5)	5 (62.5)	0.794 (0.18–3.56)	–

Note: OR were calculated with Cochran-Mantel-Haenszel test. CAO: Composite adverse outcome. 1+ of perinatal death, arterial cord pH < 7.1, admission to neonatal unit, 5-min Apgar score < 7, severe hypoglycemia requiring treatment, or CS for suspected fetal compromise.

Abbreviations: ACGV, abdominal circumference growth velocity; AOR, adjusted odds ratio; CI, confidence interval; CPR, cerebro-placental ratio; DM, diabetes mellitus; EFW, estimated fetal weight; GDM, gestational diabetes mellitus; OR, odds ratio; US RF, ultrasound risk factors.

[a]Adjusted OR was calculated with logistic regression, including EFW ≥90th centile, ACGV ≥90th centile, CPR ≤5th centile.

Table 3 shows the OR at different combinations of these independent risk factors in the total cohort on multiple logistic regression. Some increase in risk was found with a low CPR or high EFW irrespective of the other, but the greatest risk of adverse outcome was where the EFW was at the 90th centile or above and the CPR was at the 5th centile or below (OR 6.85; 95% CI 2.06–22.78).

The AUC for EFW alone was 0.542 (95% CI 0.494–0.591) and for CPR alone it was 0.525 (95% CI 0.477–0.574). The combination of these yielded an AUC of only 0.556 (95% CI 0.507–0.605).

TABLE 3 Simplified flow diagram of possible combinations of the independent ultrasound markers (EFW ≥90th centile and CPR ≤5th centile) for prediction of CAO

EFW	CPR	Fetuses N (%) 1044 (100)	CAO present N (%) 174 (16.7)	OR (95% CI)
10th–90th	≤5th	64 (6.1)	14 (8.0)	1.44 (0.78–2.66)
	>5th	845 (80.9)	126 (72.4)	1 (reference)
≥90th	≤5th	11 (1.1)	6 (3.4)	6.85 (2.06–22.78)
	>5th	124 (11.8)	28 (16.1)	1.66 (1.05–2.64)

Note: OR were calculated with Cochran-Mantel-Haenszel test. CAO: Composite adverse outcome: 1+ of perinatal death, arterial cord pH < 7.1, admission to neonatal unit, 5-min Apgar < 7, severe hypoglycemia requiring treatment, or CS for suspected fetal compromise.

Abbreviations: CI, confidence interval; CPR, cerebro-placental ratio; EFW, estimated fetal weight; OR, odds ratio.

Discussion

This analysis suggests that large for dates and low CPR are independent and mutually enhancing risk factors for adverse outcome in a pregnancy complicated by high blood glucose levels. It is the low CPR and not the abdominal circumference growth acceleration that is most associated with increased risk.

Despite this, use of these additional ultrasound factors adds little to the prediction of our CAO, with poor AUC values. This is because of multiple risk factors, particularly for such a CAO which, although similar to other studies [147], is partly dependent on other intrapartum events. Further, it is not sufficiently serious in itself to warrant screening.

Nevertheless, our analysis informs the management of macrosomic babies in hyperglycaemic pregnancy, suggesting that CPR may be worth assessing. When DM and GDM were analysed separately, no risk factor was shown to be significant. Given the reported risks associated with all three in non-diabetic pregnancy [57,94] and the significance of the risk factors when all pregnancies with high blood glucose levels are analysed together, this is likely to be a result of the small numbers involved. GDM and DM have in common abnormal glucose levels and a high incidence of macrosomia, and it is the clinical conundrum associated with this that we try to address.

The risks of a low CPR are important because the literature is sparse regarding prediction of adverse outcome in pregnancies involving pre-existing DM and GDM. Indeed, even the role and accuracy of EFW in diabetic pregnancies is not well established. The American College of Obstetricians and Gynaecologists concludes that EFW is not superior to clinical assessment in the detection of large-for-gestational-age fetuses [140]. Recently, the fetal weight centile and abdominal circumference centile were found to be relevant predictors of being large for gestational age, prematurity, and emergency CS [148] However, the presence of pre-existing DM and of a large fetus impacts negatively on the accuracy of EFW [149].

Polyhydramnios has been associated with worse maternal glycaemic control, higher concentration of amniotic fluid glucose, and larger babies [150]. Polyhydramnios increases the risk of iatrogenic preterm birth, particularly via elective CS for suspected macrosomia [151]. In our study, polyhydramnios is not associated with adverse outcome: it is possible that this depends on the exclusion of pregnancies delivered at less than 35 weeks.

Limited data on the role of the newer markers ACGV and CPR in hyperglycaemic pregnancies exist. In a study of ultrasound screening in 4512 nulliparous women, in which adjustment for maternal diabetes or gestational diabetes had minimal effect [57], a high ACGV was found to be more important than high EFW, in that suspected macrosomic babies with a normal ACGV were not at significantly increased risk of adverse outcomes, and those with the highest risk had a high ACGV and were suspected of being macrosomic. This does not align with our results, but their analysis did not include Doppler findings.

Reduced resistance in the UA and MCA, and increased resistance in the renal artery were described in 147 fetuses of pregnancies complicated by GDM [152]. In 2017, Gibbons et al demonstrated that a low CPR (below the 10th centile) was associated with increased risk of CAO in diabetic pregnancies. They did not assess the role of fetal size or ACGV, and the incidence of the CAO was 36.4% [153]. Further their results may not apply to macrosomic babies because more than one-third of their low CPR babies were SGA at birth, and very few were macrosomic. Finally, in a sample of just 130 pregnancies with GDM, Familiari et al reported that MCA PI may have a role in predicting minor adverse outcomes [154]. An inverse relation between neonatal weight and umbilical flow has been demonstrated in pregnancies complicated by type 1 diabetes and in GDM [155,156]. Umbilical pulsatility partly reflects placental resistance and this may not be the principal contributor to the vulnerability shown by diabetic pregnancies. The MCA, however, is thought to reflect brain sparing, which may be a fetal adaptation to pathology of multiple origins.

We have not evaluated the role of other ultrasound markers that have been proposed as predictors of adverse outcome in pregnancies affected by diabetes. These include the umbilical cord coiling index [157] or assessment of umbilical vein area or flow [158], as well as other biometric indexes for the evaluation of fetal soft tissues [159]. However, the use of these parameters is not yet widespread. We have decided to include standard fetal biometry, liquor volume, and basic Doppler velocimetry, as they are more commonly used in clinical practice.

The strength of this study is that almost every pregnancy had a standardized ultrasound assessment in the third trimester, with universal assessment of the CPR; however, in a few cases this was missing. Our findings remain relevant to pregnancies where CPR can be accurately measured. Some demographic data were also missing. The principal limitation of this study is its size and subsequent inability to determine the most important, serious outcomes such as death or disability. The use of a surrogate marker is therefore common in the literature and our choice is not dissimilar from other analyses: e.g., neonatal unit admission [153]; intrapartum fetal distress [153,160]. In addition to the potential limitations of amalgamation of GDM and DM pregnancies, a treatment paradox may exist because of the retrospective nature of the study and results being available to clinicians: possible risk factors influence management. This, however, might be expected to reduce the associations with adverse outcomes.

Further, this is a problem common to all but the rare prospective studies where clinicians are blinded to ultrasound findings. Since selective and not universal screening was used for the diagnosis of gestational diabetes, this cohort may not include all pregnancies in the time period but as no comparison with non-diabetic pregnancy was made, this is unlikely to have influenced our outcomes.

We have also not assessed the role of pregnancy glycaemic control. It was our intention to explore how ultrasound assessment might be improved, rather than compare it with an established cornerstone of care of a diabetic pregnancy. High third-trimester haemoglobin-A1c levels have recently been shown to be predictive of perinatal death in women with pre-existing diabetes [161]. Whether ultrasound can be used to better predict and possibly prevent such adverse outcomes is an important question.

This is the first analysis to evaluate ultrasound estimates of size, growth velocity, and Doppler together in pregnancies with high blood glucose values. It suggests that there could be benefit to assessing CPR in late pregnancy and that this may identify macrosomic babies at most risk. Although promising, much larger, and preferably prospective, analyses are required to determine its performance, and relation with markers of glycaemic control in the prediction and prevention of serious adverse outcomes.

AGA cohort

Abnormal umbilical artery pulsatility index in appropriately grown fetuses in the early third trimester: an observational cohort study

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Introduction

Stillbirth complicates 1 in 200 pregnancies in developed regions and 1 in 60 globally. Efforts to reduce stillbirth have produced modest results, with a particular focus on the identification of small-for-gestational-age (SGA) fetuses, a well-established risk factor [162]. Umbilical artery (UA) Doppler velocimetry is then used to help determine which SGA fetuses are at most risk. In "high-risk" pregnancies, this reduces perinatal mortality [127] and forms the basis of guidelines for the management of SGA [124,163]: those that are SGA with an abnormal UA pulsatility index (PI) are at sufficiently increased risk of adverse outcome that monitoring is intensive.

A common clinical problem, however, is where the fetus is not SGA, but the UA PI is nevertheless abnormal. It is generally believed that the degree of impedance to blood flow in the umbilical artery reflects the degree of placental dysfunction, and so it is biologically plausible to believe these fetuses may also be at increased risk of adverse outcomes. However, the management of such cases is unclear because the prognosis is largely unknown. More than 70% of babies with antepartum stillbirth are not SGA, particularly at term [164]. Nevertheless, risk increases with decreasing estimated fetal weight (EFW) centile, and so is related to size [54]. Growth velocity may be more important than actual size [39]. Indeed, it has been suggested that 40–60% of stillbirths have fetal growth restriction (FGR) due to placental insufficiency [165,166].

We hypothesize that appropriate-for-gestational-age (AGA) babies with an incidental finding of raised UA PI are at increased risk of adverse outcomes compared with AGA babies where the UA PI is normal.

The aim of this study was to determine if appropriate-for-gestational-age (AGA) fetuses – those that are not SGA – with a raised (>95th centile) UA PI in the early third trimester are at increased risk of placental dysfunction and adverse outcome.

Methods

This is a retrospective cohort study at a single tertiary centre at the John Radcliffe Hospital, Oxford, UK, over a 5-year period from January 2014 to September 2019. Routinely collected data were used.

Inclusion criteria were singleton pregnancies dated by crown rump length, who gave birth at the unit and had a non-anomalous fetus that had undergone a complete growth scan, with UA PI measurement, between 28 + 0 and 33 + 6 weeks' gestation. This gestation window was chosen because it is at this time that the umbilical artery is most useful in SGA babies: later, a large number of at-risk pregnancies have a normal umbilical artery Doppler [167] and the cerebroplacental ratio (CPR) is more useful [168,169].

Ultrasound at this gestation is clinically indicated, so performed only in pregnancies considered "high risk" according to local protocols, and this includes both routine and non-routine scans. Routine scans were arranged for those with accepted risk factors for FGR following local protocols based on current recommendations from Saving Babies' Lives Version 2 [170]. Routine scans were also arranged for those with pre-existing hypertensive disease requiring treatment, previous pregnancy loss after 16 weeks' gestation, gestational diabetes mellitus, pre-existing diabetes mellitus, and pre-existing medical conditions such as antiphospholipid syndrome. Non-routine scans were undertaken on an ad hoc basis for suspected or evolving pregnancy complications: local protocols dictate that non-routine can be arranged in cases of new hypertension arising in pregnancy, vaginal bleeding, symphysis-fundal height ≥ 3 cm less than the gestational age in weeks, persistent reduction in fetal movements, and any concern about fetal wellbeing subject to agreement by a senior clinician. All growth scans performed beyond 23 + 6 weeks routinely included assessment of the UA PI. From October 2016, an additional routine growth scan between 35 + 0 and 36 + 6 weeks' gestation was offered in all cases, which included an assessment of the middle cerebral artery (MCA) and cerebroplacental ratio (CPR). All scan findings were available to clinicians involved in care provision.

Management of scan findings prior to 37 + 0 weeks was according to RCOG Guidelines [163]. In situations without an established protocol (including AGA with raised UA PI) management decisions were guided by senior clinicians. After 37 + 0 weeks, all SGA babies and those with abnormal Doppler indices were risk assessed and managed according to a published algorithm [47].

Pregnancies were dated using crown rump length (CRL) before 14 weeks (except in cases of in vitro fertilization where the date of embryo transfer was available). Ultrasound examinations were conducted by accredited sonographers or clinical fellows, using Voluson E6 and E8 ultrasound machines (GE Healthcare) with a 2–

8 Hz convex probe. Measurements were recorded prospectively using commercially available archiving software (Viewpoint, GE Healthcare) and transferred using DICOM.

Doppler measurements were obtained during a period of no fetal movement, in the absence of fetal tachycardia and maintaining a low angle of insonation in a free loop of cord. The lowest PI of three satisfactory measurements was used. EFW was calculated from head circumference, abdominal circumference and femur length measurements using Hadlock's 1985 equation [46]. The gestation specific z-score for EFW was calculated according to the method described by Hadlock, and AGA was defined as EFW ≥10th centile [171]. Scan reports presented the UA PI centile according to Acharya to clinicians [172]. However, for the purposes of analysis, the gestation specific z-score for UA PI was calculated according to the method described by Ciobanu, and abnormal UA PI was defined as > 95th centile [145]. For outcomes, birth weight was defined using UK 90 standards [173]; CPR < 5th centile was defined using equations from Ciobanu et al. [145], and fetal growth restriction (FGR) according to ISUOG Consensus Criteria [44]. Data were collected prospectively and merged according to a unique identifier from neonatal (Badgernet), maternity (Cerner) and ultrasound (Viewpoint, GE Healthcare) records.

Two groups of pregnancies were compared (Appendix A). AGA fetuses with an UA PI $>95^{th}$ centile at any scan during the target gestation window were allocated to group 1. The first scan with such findings was assessed. Pregnancies where any previous scans showed the fetus to be SGA were excluded, but those where any subsequent scan showed SGA were not. Group 2 comprised pregnancies scanned in the same gestation window where the fetus was AGA but with an UA PI $\leq 95^{th}$ centile at all scans performed during the window.

Appendix A. Terms and definitions.

Term/group	Definition
Index scan	An ultrasound scan taking place between 28 + 0 and 33 + 6 weeks' gestation where complete biometry (head circumference, abdominal circumference, and femur length) and UA PI results were available. Where more than one scan met these criteria, the scan closest to 33 + 6 was treated as the index scan.
Group 1	Cases were allocated to group 1 if they had a scan with complete biometry between 28 + 0 and 33 + 6 showing EFW ≥10th centile with UA PI >95th centile, provided they had not previously had an EFW <10th centile on any earlier scan from 28 + 0 onwards.
Group 2	Cases were allocated to group 2 if they had a scan with complete biometry between 28 + 0 and 33 + 6 showing EFW ≥ 10th centile with UA PI ≤95th centile, and never had UA PI >95th centile or EFW <10th centile in this gestational window.

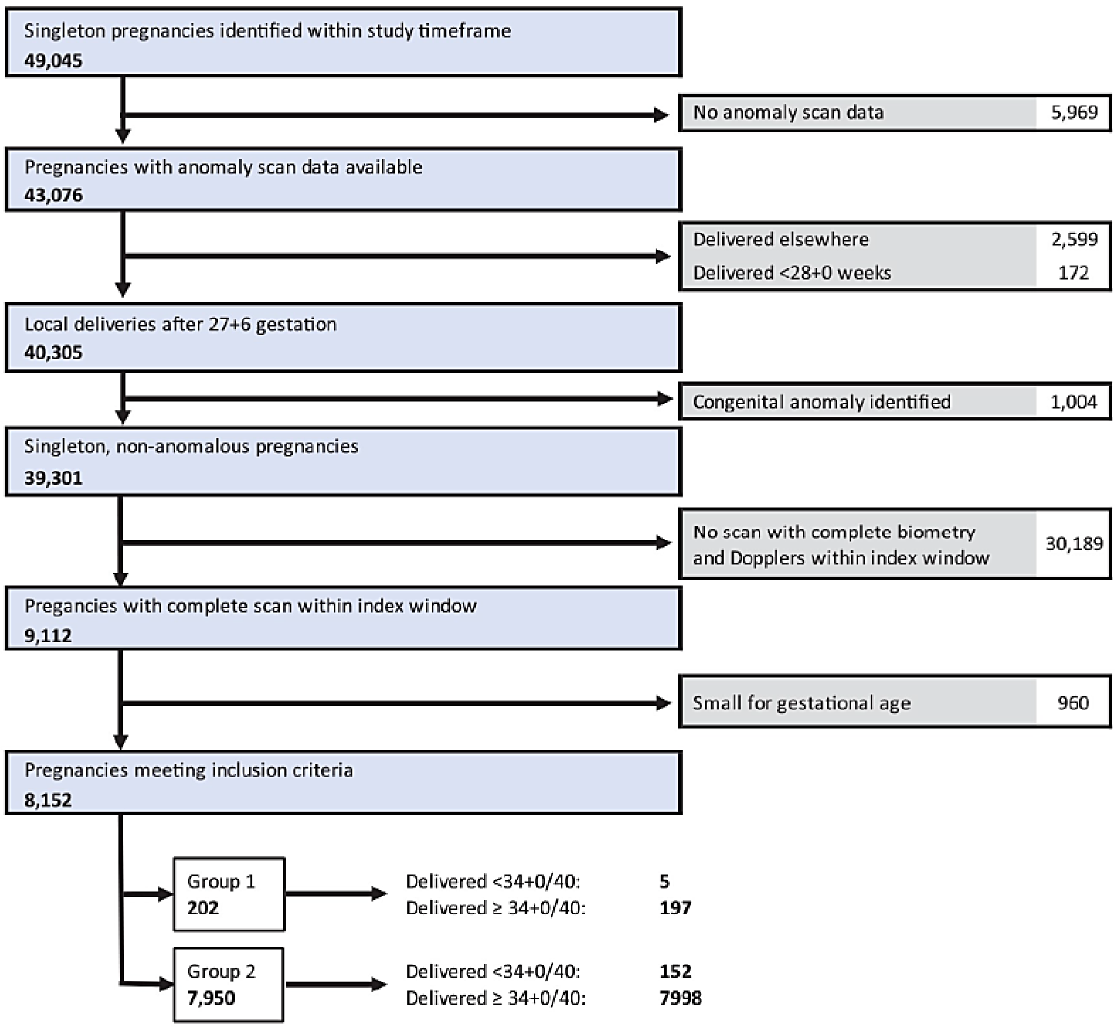
STROBE guidelines were followed. Analysis was performed using SPSS (version 26). Demographic characteristics, ultrasound findings and pregnancy, birth and neonatal outcomes were summarized in the two groups with median and interquartile range (IQR) for continuous variables and count and proportion for categorical variables, and compared by means of Mann-Whitney U test or chi-square test as appropriate.

Where missing values occurred, calculations were performed using only pregnancies with data as the denominator. Differences between the two groups were compared using odds ratios (OR), with 95% confidence intervals. Logistic regression was used to adjust for covariates and adjusted odds ratios were calculated. Two regressions were performed: the first using EFW z-score at the time of the index scan as a covariate, and the second using labour induction and gestational age at delivery. This was performed to investigate the effect of EFW z-score at the time of the index scan, as well as timing and mode of birth, on the outcomes of interest. Ethical approval was granted on 27/07/2017: (IRAS project ID 222260; REC reference: 17/SC/0374).

Results

Of 9112 eligible pregnancies, 202 (2.2%) met criteria for Group 1 and 7950 (87.3%) for Group 2 (the reference group) (Appendix C). The remaining 960 (10.5%) pregnancies were SGA and were excluded. No babies in Group 1 had absent/reversed end diastolic flow in the umbilical artery at the index scan.

Appendix C. Summary of exclusions and group allocation.



Demographic and index scan details are presented in Appendix D. The proportion of smokers was higher in Group 1 ($p < .001$), the median maternal age was younger (p < .001), but there were no other significant demographic differences. The index scans were performed at a similar gestation in both groups (30 weeks' gestation). EFW z-score was significantly lower in group 1 (p < .001), and growth velocity (change in z-score since anomaly scan/days since anomaly scan) was also significantly lower (p < .001); showing that Group 1, although still AGA, were smaller and had slower apparent growth since the anomaly scan. Induction of labour was more common in group 1 (p .03) and the median gestational age at birth for group 1 was two days earlier than group 2 (p .004). Although statistically significant, the observed difference in gestational age at birth is unlikely to be of clinical significance.

Appendix D. Cohort characteristics.

	Median (IQR) or *n* (%)			
Characteristics	Group 1 *N* = 202	Group 2 *N* = 7950	Missing	*p*-Value
Demographic details				
Age	30 (26–34)	32 (28–36)		<.001
Height (cm)	164 (160–68)	165 (160–170)	94	.125
Weight at booking (kg)	65 (54.5–75.5)	68 (57–79)	113	.219
Body mass index at booking	24.36 (20.26–28.47)	24.80 (20.85–28.75)	125	.448
Nulliparity	90 (44.6)	3133 (39.4)		.14
Smoker at booking	54 (27.3)	1176 (15.1)	187	<.001
Assisted reproductive techniques	6 (3.0)	369 (4.6)		.26
Ethnicity				.36
Asian	12 (5.9)	615 (7.7)		
Black	3 (1.5)	163 (2.1)		
Mixed race	7 (3.5)	148 (1.9)		
White	135 (66.8)	5140 (64.7)		
Other	0	60 (0.8)		
Not stated	45 (22.3)	1824 (22.9)		

(*continued*)

Appendix D. Continued.

Characteristics	Median (IQR) or *n* (%)		Missing	*p*-Value
	Group 1 $N = 202$	Group 2 $N = 7950$		
Medical background				
Preexisting diabetes mellitus	3 (1.5)	220 (2.8)		.27
Gestational diabetes mellitus	26 (12.9)	1321 (16.6)		.16
Hypertensive disease	25 (12.5)	764 (9.6)		.19
Index scan findings				
Gestational age (days)	210 (197–224)	208 (195–221)		.592
EFW z-score	−0.32 (−0.87 to 0.23)	−0.09 (−0.58 to 0.40)		<.001
Growth velocity[a]	−0.002 (−0.007 to 0.003)	0.0001 (−0.0049 to 0.0051)		<.001
Mean UA PI z-score	1.67 (1.22–2.12)	−0.03 (−0.70 to 0.64)		<.001
Labor and delivery				
Gestational age at birth (days)	274 (254–283)	276 (269–283)		.004
Labor induction	78 (38.6)	2509 (31.6)		.03
Prelabor cesarean section	12 (5.9)	390 (4.9)		.50
Intrapartum cesarean section	23 (11.4)	858 (10.8)		.79

[a]Change in z-score since anomaly scan/days since anomaly scan.

Group 1 had a significantly increased risk of being born SGA (OR 3.94, CI 2.80–5.53), including severe SGA (OR 4.91, CI 2.65–9.08), and being born preterm (OR 1.71, CI 1.13–2.58). The risk of SGA remained after adjustment for the EFW z score at the index scan (OR 2.43, CI 1.64–3.59), suggesting that it was not simply because these babies were smaller to start with. There was no difference in adverse outcomes, including after adjustment for intervention (Table 1).

Table 1. Perinatal outcomes.

Outcome	*N* (%)		OR (95% CI)	AOR1	AOR2
	Group 1 $N = 202$	Group 2 $N = 7950$			
Birthweight <10th centile	46 (22.8)	554 (7.0)	3.94 (2.80–5.53)	2.43 (1.64–3.59)	4.05 (2.87–5.70)
Birthweight <3rd centile	12 (5.9)	101 (1.3)	4.91 (2.65–9.08)	2.10 (1.05–4.21)	4.81 (2.59–8.92)
Extended perinatal mortality	1 (0.5)	24 (0.3)	1.64 (0.22–12.21)	1.72 (0.23–12.82)	1.27 (0.17–9.62)
CAO[a]	28 (13.9)	876 (11)	1.30 (0.87–1.95)	1.44 (0.96–2.16)	1.02 (0.64–1.61)
Severe CAO[b]	34 (16.8)	1641 (20.6)	0.78 (0.54–1.13)	0.79 (0.55–1.15)	0.74 (0.49–1.04)
Birth < 34/40	5 (2.5)	152 (1.9)	1.30 (0.53–3.21)	1.17 (0.47–2.90)	
Birth < 37/40	27 (13.4)	658 (8.3)	1.71 (1.13–2.58)	1.83 (1.21–2.77)	
Intrapartum cesarean section	23 (11.4)	858 (10.8)	1.06 (0.68–1.65)	1.14 (0.73–1.77)	0.98 (0.62–1.54)

[a]CAO (Composite adverse outcome): Apgar score <7 at 5 min, neonatal unit admission, cord arterial pH <7.1. [b]Severe CAO (severe composite adverse outcome): Extended perinatal mortality, Apgar score <4 at 5 min, base excess <= −12, cord arterial pH <7.0, hypoxic ischaemic encephalopathy, ventilated >24 h, sepsis. AOR1: adjusted for EFW z-score at index scan. AOR2: adjusted for labor induction and gestational age at delivery.

Of the 8152 pregnancies, 4550 (55.8%) continued beyond 34 + 0 weeks and had at least one further complete growth scan (Table 2). Group 1 pregnancies were not more likely to undergo a further scan, but had significantly higher rates of SGA (OR 6.76, CI 4.23–10.80), severe SGA (OR 13.32, CI 6.59–26.91), and FGR (OR 9.85, CI 6.27–15.49) according to the ISUOG Delphi consensus definition [44]. In some cases, Doppler velocimetry was repeated without fetal biometry: of the 4606 (56.5%) cases that continued beyond 34 + 0 and had both UA and MCA Doppler measurements repeated, UA PI was significantly more likely to be > 95th centile (OR 18.79, CI 11.51–30.66), and the CPR was more likely to be < 5th centile (OR 5.07, CI 3.37–7.63). This effect was little altered by adjustment for EFW at the index scan. MCA PI was also more likely to be <5th centile, but this effect was not statistically significant.

Table 2. Findings of final ultrasound scans ≥34 weeks.

Final ultrasound scan findings	N (%) Group 1 (N = 202)	N (%) Group 2 (N = 7950)	OR (95% CI)	AOR (95% CI)
Had growth scan ≥34 + 0	112 (55.4)	4438 (55.8)	0.99 (0.75–1.30)	
EFW <10th centile at final growth scan	25 (22.3)	181 (4.1)	6.76 (4.23–10.80)	6.19 (3.61–10.61)
EFW <3rd centile at final growth scan	11 (9.8)	36 (0.8)	13.32 (6.59–26.91)	10.59 (4.94–22.68)
ISUOG FGR criteria met at final scan	29 (25.9)	152 (3.4)	9.85 (6.27–15.49)	8.80 (5.40–14.34)
Had further UmbA and MCA Doppler assessment ≥ 34 + 0	114 (56.4)	4492 (56.5)	1.00 (0.75–1.32)	
UmbA PI >95th	27 (23.7)	73 (1.6)	18.79 (11.51–30.66)	15.51 (10.02–27.19)
MCA PI <5th centile	17 (14.9)	535 (11.9)	1.30 (0.79–2.19)	1.29 (0.77–2.19)
CPR <5th centile	36 (31.6)	375 (8.3)	5.07 (3.37–7.63)	4.91 (3.26–7.39)

AOR: Adjusted for EFW z-score at time of index scan.

Discussion

These findings suggests that a raised UA PI in an early third trimester AGA fetus is associated with subsequent development of FGR markers and increased risk of severe birth weight SGA. This is independent of the lower mean EFW of these babies: these fetuses are not merely smaller but they are at risk of deterioration in growth and placental function. Indeed, this slowed growth has already started at the time of the index scan.

It was not our remit to determine whether and to what extent umbilical artery Doppler can be used to screen for SGA or adverse outcomes. We wished to inform practice when faced with the relatively common conundrum of Group 1. The lack of association with adverse outcomes may be because these outcomes are relatively rare or could be due to intervention; and this is reflected in the higher rates of preterm birth, labour induction, and caesarean section. These fetuses do not appear to be at immediate risk and may not require monitoring at intervals appropriate for an SGA baby with an abnormal UA PI. Yet we conclude that such a finding necessitates further assessment for FGR as it is associated with an increased risk of markers of long term adverse neonatal outcome.

This finding aligns with the relatively sparse literature. Goffinet et al. examined 192 AGA fetuses with an UA resistance index > 90th centile of the study population, which comprised 2016 low-risk pregnancies scanned at 28 weeks between 1988 and 1990 [174]. Raised UA resistance index was associated with a 2 and 3-fold increase in birth weight below the 10th and 3rd centiles respectively. These 30-year-old data are consistent with our findings. Key differences are the low-risk population, the likely poorer accuracy of ultrasound because of subsequent improvements in technology, and the different reference ranges.

Al Hamayel et al., in a study of fetuses with an EFW >10th centile, compared 98 women who had a raised UA PI to 2646 who did not [175]. They found a 2-fold increase in the risk of SGA at birth, although the gestation at assessment was unclear. Valino et at (2016), in a screening study of 8268 pregnancies, show that abnormal UA PI at 30–34 weeks was a risk factor for subsequent low birth weight that was independent of the EFW [176]. In a retrospective study of 2485 pregnancies, Khalil et al. demonstrated that among term births with Doppler assessment at 34 + 0 to 35 + 6 (later than in our study), UA PI was higher among babies requiring neonatal unit admission, despite no difference in EFW percentile [177]. Mone et al. further showed that an abnormal UA in AGA fetuses at 28 weeks, although not at 32 and 34 weeks, was associated with impaired cognitive assessments of information processing and memory [178].

More recently, systematic review and meta-analysis has assessed fetal umbilical artery Doppler velocimetry as a tool for universal screening in the third trimester and the authors conclude that UA Doppler has moderate predictive accuracy for birth weight SGA, but not for indicators of neonatal morbidity [179]. However, outside of the context of universal screening, this does not address the significance of abnormal UA PI with AGA in a clinically indicated third trimester scan.

Our findings add weight to the increasing emphasis on FGR rather than on cut-offs of absolute EFW. Reliance on SGA alone in the early third trimester risks missing a small cohort of babies who later develop established risk factors for serious adverse outcomes. While our evidence is not sufficient to recommend universal screening in an unselected population, it suggests that UA velocimetry does have utility whenever ultrasound assessment of fetal growth is indicated, including for babies that are not SGA.

This study is strengthened by its relatively large sample, prospective data collection and use of DICOM to prevent transcription errors. Our comparison groups were carefully specified, with index scans at similar gestations and with a similar frequency of subsequent scans.

We nevertheless acknowledge potential limitations. We used cut-offs of umbilical artery Doppler rather than a continuous variable: this was to directly address the question posed. Our numbers were insufficient to examine serious adverse events of antepartum origin; this further prevented us from analysing whether Group 1 had different outcomes from Group 2 according to whether they had had a further scan. The length of the study (>5 years) means that local practice changed during the study timeframe. Specifically, a routine growth scan between 35 + 0 and 36 + 6 weeks' gestation was introduced, although, since allocation to Group 1 and 2 is independent of this factor, this should not be a source of bias. The study population was not unselected, in that the index scans were clinically indicated, and findings should not necessarily be applied to situations where universal screening of low-risk women at this gestation is undertaken. Equally, our findings are likely therefore more translatable to a general obstetric population without universal ultrasound in the early third trimester, and our rate of ultrasound (23.2%) was not dissimilar to the proportion of clinically indicated scans in a recent UK study [180]. Finally, not all pregnancies with a raised UA had a repeat assessment, likely because the reference chart used for analysis [145] was more up-to date than that used for clinical decision making [172]. This meant that the UA PI centiles presented to clinicians at the time were slightly different to those presented in this study, but this also has the advantage of helping to reduce the effects of intervention paradox since the PI value representing the 95th centile is lower for the new charts [145].

We conclude that raised UA PI in AGA fetuses in the early third trimester is associated with increased risk of both birth weight SGA and other late pregnancy markers of abnormal placental function.

Summary of findings and conclusions

Assessment of fetal growth is a pillar of the antenatal care as fetal size and growth trajectories are important indicators of underlying fetal health. Both extremes of fetal growth are associated with an increased incidence of adverse perinatal outcomes and long term sequelae.

For instance, pathological fetal growth restriction (FGR) may cause cardiovascular remodelling and other developmental adaptations that protect the fetus in utero but increase the risks of neonatal morbidity and long-term health consequences [181,182]. FGR is associated with stillbirth, prolonged neonatal hospitalization, feeding and respiratory difficulties, abnormal brain development, long term cardiovascular disease, developmental delay, and early mortality [115].

FGR fetuses do not reach their biological growth potential as a consequence of impaired placental function, which may be because of a variety of factors. Small-for-gestational age (SGA), defined as fetal weight/birth weight below the 10th centile for gestational age, is commonly used as a proxy for FGR. SGA, however, differs from FGR principally because it also encompasses a majority of constitutionally small but healthy fetuses at lower risk of abnormal perinatal outcome. On the other hand, growth-restricted fetuses with biometry > 10th centile may not meet their growth potential, and may remain undiagnosed despite being at increased risk of adverse outcome [44]. From both a clinical and a scientific perspective, it is most relevant to focus on fetuses that are at risk for adverse outcome, highlighting the need for a clear definition of FGR distinct from SGA.

This research project demonstrated that several parameters, including sequential ultrasound measurements focusing on declining/crossing growth centiles, functional parameters such as Doppler waveform analysis (umbilical artery (UA), fetal middle cerebral artery and CPR), and pregnancy characteristics allow risk stratification and identification of growth restricted fetuses at increased risk of adverse outcomes.

A prescriptive protocol for management of SGA fetuses, including risk stratification with conservative management for those considered at low risk, allows fewer interventions to be accompanied by less neonatal morbidity. Nevertheless, such a protocol determines improvement in maternal outcomes with significantly more pregnancies reaching 39 weeks, going into labour spontaneously and, when delivery was considered indicated, to not be delivered by caesarean section. This is also followed by a considerable reduction in NNU admission.

We demonstrated that in near-term fetuses diagnosed antenatally as SGA, a reduction (< 10^{th} centile) in ACGV between 20 and 36 weeks is a risk factor for adverse outcome that is independent of EFW and CPR. Estimation of fetal weight in the third trimester alone is an inadequate screening test for adverse perinatal outcome. Our findings suggest that using ACGV in addition to EFW and CPR will improve risk stratification of near-term SGA fetuses and might improve the prediction of adverse outcome in SGA fetuses.

We identified nine SGA clinical phenotypes associated with significantly different patterns of risk for adverse perinatal outcome. Using easily obtainable clinical information, in addition to commonly accepted SGA clinical phenotypes (IUGR, constitutional SGA and congenital anomaly), we identified six clinical phenotypes (preterm birth, hypertension/PE, assisted reproduction technique, chronic maternal disease, gestational diabetes and second or third-trimester bleeding), which are associated with a significantly increased risk of adverse perinatal outcome. In our study cohort these fetuses, which would have been considered low-risk SGA according to current classification systems, accounted for three of four perinatal deaths outside the IUGR and congenital anomaly clusters. Focusing on clinical management of SGA, three practical conclusions can be derived from our findings.

First, according to international consensus, SGA fetuses without congenital anomaly and with normal Doppler findings should be monitored closely, with delivery near term [69,120]. However, when considering other clinical conditions in addition to abnormality on Doppler or ultrasound, we identified a group of fetuses with a significantly worse perinatal outcome compared with AGA fetuses. Second, exclusion of the SGA fetuses with other clinical conditions reduced considerably the perinatal risk of the remaining SGA fetuses. Third, it is important to highlight the increased risk when SGA is accompanied by other obstetric pathologies. This findings suggest that considering clinical characteristics in addition to ultrasound examination findings may improve risk stratification and decision-making for management of SGA fetuses.

On the other hand, fetal macrosomia may lead to poor placental function [141], maladaptive endocrinologic and cardiovascular responses. LGA fetuses, especially those of diabetic mothers, have different body proportions, fat deposition, and metabolic profiles, resulting in increased risks of shoulder dystocia and neonatal hypoglycaemia [183,184]. In the long term, macrosomia or large for gestational age birth weight may confer increased risks of childhood obesity, insulin resistance, or overt diabetes, all of which contribute to poorer health [183,185].

We demonstrated that large for dates and low CPR are independent and mutually enhancing risk factors for adverse outcome in a pregnancy complicated by high blood glucose levels. In addition, low CPR and not the abdominal circumference growth acceleration is most associated with increased risk. Despite this, use of these additional ultrasound factors adds little to the prediction of composite adverse outcome (CAO), with poor AUC values. This is because of multiple risk factors, particularly for such a CAO which, although similar to other studies [147], is partly dependent on other intrapartum events. However, these findings suggest that there could be benefit to assessing CPR in late pregnancy complicated by high blood glucose levels as this may allow identification of macrosomic babies at most risk.

Another common clinical problem is where the fetus is not SGA, but the umbilical artery pulsatility index is nevertheless abnormal. It is generally believed that the degree of impedance to blood flow in the umbilical artery reflects the degree of placental dysfunction, and so it is biologically plausible to believe these fetuses may also be at increased risk of adverse outcomes. However, the management of such cases is unclear because the prognosis is largely unknown. More than 70% of babies with antepartum stillbirth are not SGA, particularly at term [164].

We demonstrated that a raised UA PI in an early third trimester AGA fetus is associated with subsequent development of FGR markers and increased risk of severe birth weight SGA. This is independent of the lower mean EFW of these babies: these fetuses are not merely smaller but they are at risk of deterioration in growth and placental function. Indeed, this slowed growth has already started at the time of the index scan. These fetuses do not appear to be at immediate risk and may not require monitoring at intervals appropriate for an SGA baby with an abnormal UA PI. Yet we conclude that such a finding necessitates further assessment for FGR as it is associated with an increased risk of markers of long term adverse neonatal outcome.

This project emphasises the importance of developing algorithms, based on pregnancy characteristics, assessment of growth trajectory, fetal size, Doppler indices and biomarkers, to allow better identification of fetuses at risk rather than merely focus on cut-offs of absolute EFW. Reliance on EFW alone in the early third trimester risks missing a cohort of babies who later develop established risk factors for serious adverse outcomes.

According to the results obtained and previously discussed, the main conclusions of our research project are:

1. A prescriptive protocol for management of SGA fetuses, including risk stratification with conservative management for those considered at low risk, allows fewer interventions to be accompanied by less neonatal and maternal morbidity.
2. In near-term fetuses diagnosed antenatally as SGA, a reduction (< 10^{th} centile) in ACGV between 20 and 36 weeks is a risk factor for adverse outcome that is independent of EFW and CPR.

3. In addition to commonly accepted SGA clinical phenotypes (IUGR, constitutional SGA and congenital anomaly), we identified six clinical phenotypes (preterm birth, hypertension/PE, assisted reproduction technique, chronic maternal disease, gestational diabetes and second or third-trimester bleeding), which are associated with a significantly increased risk of adverse perinatal outcome.
4. LGA and low CPR are independent and mutually enhancing risk factors for adverse outcome in a pregnancy complicated by high blood glucose levels.
5. A raised umbilical artery PI in an early third trimester AGA fetus is associated with subsequent development of FGR markers and increased risk of low birth weight.

Resumen de resultados y conclusiones

La evaluación del crecimiento fetal es un pilar de la atención prenatal, ya que el tamaño y las trayectorias de crecimiento del feto son indicadores importantes de la salud fetal subyacente. Ambos extremos del crecimiento fetal se asocian con una mayor incidencia de resultados perinatales adversos y secuelas a largo plazo.

Por ejemplo, la restricción patológica del crecimiento fetal (FGR) puede causar remodelación cardiovascular y otras adaptaciones del desarrollo que protegen al feto en el útero pero aumentan los riesgos de morbilidad neonatal y consecuencias para la salud a largo plazo [181,182]. La FGR se asocia con muerte fetal, hospitalización neonatal prolongada, dificultades respiratorias y de alimentación, desarrollo cerebral anormal, enfermedades cardiovasculares a largo plazo, retraso en el desarrollo y mortalidad temprana [115].

Los fetos FGR no alcanzan su potencial de crecimiento biológico como consecuencia de una función placentaria deteriorada, lo que puede deberse a una variedad de factores. Los fetos pequeños para su edad gestacional (SGA), definido como el peso fetal/peso al nacer por debajo del 10 percentil para la edad gestacional, se utiliza comúnmente como indicador de la FGR. Sin embargo, SGA difiere de FGR principalmente porque también abarca una mayoría de fetos constitucionalmente pequeños pero sanos con menor riesgo de resultados perinatales anormales. Por otro lado, los fetos con crecimiento restringido con biometría >10 percentil pueden no alcanzar su potencial de crecimiento y pueden permanecer sin diagnosticar a pesar de tener un mayor riesgo de resultados adversos [44]. Tanto desde una perspectiva clínica como científica, es más relevante centrarse sobre fetos que corren riesgo de sufrir resultados adversos, destacando la necesidad de una definición clara de FGR distinta de SGA.

Este proyecto de investigación demostró que varios parámetros, incluidas las mediciones de ultrasonido secuenciales que se centran en percentiles de crecimiento decrecientes o cruzados, parámetros funcionales como el análisis de la forma de onda Doppler (arteria umbilical (UA), arteria cerebral media fetal y CPR) y las características del embarazo permiten la estratificación e identificación del riesgo. de fetos con crecimiento restringido corren mayor riesgo de sufrir resultados adversos.

Un protocolo prescriptivo para el tratamiento de fetos SGA, que incluya la estratificación del riesgo con un tratamiento conservador para aquellos considerados de bajo riesgo, permite que menos intervenciones vayan acompañadas de una menor morbilidad neonatal. Sin embargo, un protocolo de este tipo determina una mejora en los resultados maternos con un número significativamente mayor de embarazos que llegan a las 39 semanas, que entran en trabajo de parto de forma espontánea y, cuando el parto se considera indicado, no se realizan por cesárea. A esto también le sigue una reducción considerable de las admisiones a la unidad neonatal.

Demostramos que en fetos a corto plazo diagnosticados prenatalmente como SGA, una reducción (< 10 percentil) en el ACGV entre las 20 y 36 semanas es un factor de riesgo de resultados adversos que es independiente del EFW y la CPR. La estimación del peso fetal por sí sola en el tercer trimestre es una prueba de detección inadecuada para detectar resultados perinatales adversos. Nuestros hallazgos sugieren que el uso de ACGV además de EFW y CPR mejorará la estratificación del riesgo de fetos SGA a corto plazo y podría mejorar la predicción de resultados adversos en fetos SGA.

Identificamos nueve fenotipos clínicos SGA asociados con patrones de riesgo significativamente diferentes de resultados perinatales adversos. Utilizando información clínica fácilmente obtenible, además de los fenotipos clínicos SGA comúnmente aceptados (IUGR, SGA constitucional y anomalía congénita), identificamos seis fenotipos clínicos (parto prematuro, hipertensión/PE, técnica de reproducción asistida, enfermedad materna crónica, diabetes gestacional y segunda o sangrado del tercer trimestre), que se asocian con un riesgo significativamente mayor de resultados perinatales adversos. En nuestra cohorte de estudio, estos fetos, que se habrían considerado SGA de bajo riesgo según los sistemas de clasificación actuales, representaron tres de cuatro muertes perinatales fuera de los grupos de IUGR y anomalías congénitas. Centrándonos en el tratamiento clínico del SGA, se pueden derivar tres conclusiones prácticas de nuestros hallazgos.

En primer lugar, según el consenso internacional, los fetos SGA sin anomalías congénitas y con Doppler normales deben ser monitoreados de cerca, con un parto cercano al término [69,120]. Sin embargo, al considerar otras condiciones clínicas además de las anomalías en el Doppler o la ecografía, identificamos un grupo de fetos con un resultado perinatal significativamente peor en comparación con los fetos AGA. En segundo lugar, la exclusión de los fetos SGA con otras condiciones clínicas redujo considerablemente el riesgo perinatal de los fetos SGA restantes. En tercer lugar, es importante resaltar el mayor riesgo cuando el SGA se acompaña de otras patologías obstétricas. Estos hallazgos sugieren que considerar las características clínicas además de los hallazgos del examen ecográfico puede mejorar la estratificación del riesgo y la toma de decisiones para el manejo de fetos SGA.

Por otro lado, la macrosomía fetal puede provocar una función placentaria deficiente [141] y respuestas endocrinológicas y cardiovasculares desadaptativas. Los fetos LGA, especialmente los de madres diabéticas, tienen diferentes proporciones corporales, deposición de grasa y perfiles metabólicos, lo que resulta en un mayor riesgo de distocia de hombros e hipoglucemia neonatal

[183,184]. A largo plazo, la macrosomía o el peso al nacer grande para la edad gestacional pueden conferir mayores riesgos de obesidad infantil, resistencia a la insulina o diabetes manifiesta, todo lo cual contribuye a una peor salud [183,185].

Demostramos que las fechas elevadas y la CPR baja son factores de riesgo independientes y que se potencian mutuamente para un resultado adverso en un embarazo complicado por niveles altos de glucosa en sangre. Además, la CPR baja y no la aceleración del crecimiento de la circunferencia abdominal es la que más se asocia con un mayor riesgo. A pesar de esto, el uso de estos factores ecográficos adicionales aporta poco a la predicción del resultado adverso compuesto (CAO), con valores deficientes de AUC. Esto se debe a múltiples factores de riesgo, particularmente para tal CAO que, aunque similar a otros estudios [147], depende en parte de otros eventos intraparto. Sin embargo, estos hallazgos sugieren que podría ser beneficioso evaluar la CPR al final del embarazo complicado por niveles altos de glucosa en sangre, ya que esto puede permitir la identificación de bebés macrosómicos con mayor riesgo.

Otro problema clínico común es cuando el feto no es SGA, pero el índice de pulsatilidad de la arteria umbilical es anormal. En general, se cree que el grado de impedancia al flujo sanguíneo en la arteria umbilical refleja el grado de disfunción placentaria, por lo que es biológicamente plausible creer que estos fetos también pueden tener un mayor riesgo de sufrir resultados adversos. Sin embargo, el tratamiento de estos casos no está claro porque el pronóstico es en gran medida desconocido. Más del 70% de los bebés con muerte fetal antes del parto no son SGA, especialmente a término [164].

Demostramos que un PI de la arterial umbilical elevada en un feto AGA temprano en el tercer trimestre se asocia con el desarrollo posterior de marcadores FGR y un mayor riesgo de SGA con peso grave al nacer. Esto es independiente del EFW medio más bajo de estos bebés: estos fetos no sólo son más pequeños sino que también corren el riesgo de sufrir un deterioro en el crecimiento y la función placentaria. De hecho, esta desaceleración del crecimiento ya había comenzado en el momento del análisis del índice. Estos fetos no parecen estar en riesgo inmediato y es posible que no requieran monitoreo a intervalos apropiados para un bebé SGA con una UA PI anormal. Sin embargo, llegamos a la conclusión de que tal hallazgo requiere una evaluación adicional de la FGR, ya que se asocia con un mayor riesgo de marcadores de resultados neonatales adversos a largo plazo.

Este proyecto enfatiza la importancia de desarrollar algoritmos, basados en las características del embarazo, la evaluación de la trayectoria de crecimiento, el tamaño fetal, los índices Doppler y los biomarcadores, para permitir una mejor identificación de los fetos en riesgo en lugar de centrarse simplemente en los puntos de corte del EFW absoluto. Depender únicamente del EFW a principios del tercer trimestre corre el riesgo de perder una cohorte de bebés que luego desarrollan factores de riesgo establecidos para resultados adversos graves.

De acuerdo con todo lo anteriormente expuesto, las conclusiones principales de nuestro proyecto de investigación, de acuerdo con los resultados obtenidos son:

1. Un protocolo prescriptivo para el tratamiento de fetos SGA, que incluya la estratificación del riesgo con un tratamiento conservador para aquellos considerados de bajo riesgo, permite que menos intervenciones vayan acompañadas de una menor morbilidad maternal and neonatal.
2. En fetos a corto plazo diagnosticados prenatalmente como SGA, una reducción (< 10 percentil) en el ACGV entre las 20 y 36 semanas es un factor de riesgo de resultados adversos que es independiente del EFW y la CPR.
3. Además de los fenotipos clínicos SGA comúnmente aceptados (IUGR, SGA constitucional y anomalía congénita), identificamos seis fenotipos clínicos (parto prematuro, hipertensión/PE, técnica de reproducción asistida, enfermedad materna crónica, diabetes gestacional y segunda o sangrado del tercer trimestre), que se asocian con un riesgo significativamente mayor de resultados perinatales adversos.
4. Las fechas elevadas y la CPR baja son factores de riesgo independientes y que se potencian mutuamente para un resultado adverso en un embarazo complicado por niveles altos de glucosa en sangre.

5. Un PI de la arterial umbilical elevada en un feto AGA temprano en el tercer trimestre se asocia con el desarrollo posterior de marcadores FGR y un mayor riesgo de SGA con peso grave al nacer.

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Approval by ethical committees

CEICA (Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón) certificate for the study:

- Ruiz-Martinez S, Delgado JL, Paules C, Cavallaro A, De Paco C, Villar J, Papageorghiou A, Oros D. Clinical phenotypes for risk stratification in small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2022; 59: 490–496. PMID: 34396614.

Certificate of Health Research Authority (HRA) Approval for the studies:

- Veglia M, Cavallaro A, Papageorghiou A, Black R, Impey L. Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol. Ultrasound Obstet Gynecol. 2018 Jul; 52(1):66-71. PMID: 28600829.

- Cavallaro A, Veglia M, Svirko E, Vannuccini S, Volpe G, Impey L. Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2018 Oct; 52(4):494-500. PMID: 29266519.

- Garbagnati M, Aye C, Cavallaro A, Mathewlynn S, Ioannou C, Impey L. Ultrasound predictors of adverse outcome in pregnancy complicated by pre-

existing and gestational diabetes. Acta Obstet Gynecol Scand. 2022 Jul; 101(7):787-793. PMID: 35441701.

- Mathewlynn S, Beriwal S, Ioannou C, Cavallaro A, Impey L. Abnormal umbilical artery pulsatility index in appropriately grown fetuses in the early third trimester: an observational cohort study. J Matern Fetal Neonatal Med. 2022 Dec 8; 1-8. PMID: 36482725.

GOBIERNO DE ARAGON
Departamento de Sanidad

C.P. - C.I. PI19/303

24 de julio de 2019

Dña. María González Hinjos, Secretaria del CEIC Aragón (CEICA)

CERTIFICA

1º. Que el CEIC Aragón (CEICA) en su reunión del día 24/07/2019, Acta Nº 14/2019 ha evaluado la propuesta del investigador referida al estudio:

Título: Valores de normalidad ecográficos de la hemodinámica fetal. Proyecto FETHUS

Investigadora Principal: Sara Ruiz Martínez, HCU Lozano Blesa

Versión protocolo: Versión 2.0 (09.07.2019)
Versión documento de información y consentimiento: Versión 2.0 (09.07.2019)

2º. Considera que

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuada la utilización de los datos y los documentos para obtener el consentimiento informado.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los Investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

3º. Por lo que este CEIC emite **DICTAMEN FAVORABLE a la realización del estudio**.

Lo que firmo en Zaragoza

GONZALEZ HINJOS MARIA - DNI 03857456B

Firmado digitalmente por GONZALEZ HINJOS MARIA - DNI 03857456B
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Secretaria del CEIC Aragón (CEICA)

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NHS
Health Research Authority

Mr Lawrence Impey
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Level 6, Womens Centre, John Radcliffe Hospital, Headley Way
Headington, Oxford
OX3 9DU

Email: hra.approval@nhs.net

27 July 2017

Dear Mr Impey

Letter of HRA Approval

Study title:	**Investigating the structured use of ultrasound scanning for fetal growth (Oxford Growth Restriction Identification Programme (OxGRIP)) on risk factors for and the incidences of adverse maternal, fetal and neonatal outcomes.**
IRAS project ID:	**222260**
REC reference:	**17/SC/0374**
Sponsor	**R&D Lead**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **222260**. Please quote this on all correspondence.

Yours sincerely

Miss Lauren Allen
Assessor

Email: hra.approval@nhs.net

Copy to: *Heather House, R&D Lead (Sponsor contact & Lead NHS R&D contact)*

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_11072017]		11 July 2017
Letter from sponsor [Sponsor letter]		23 June 2017
Other [OSPREA Patient letter]	v5	05 January 2016
Referee's report or other scientific critique report [Independent review]		21 April 2017
Research protocol or project proposal [OxGRIP Protocol V1]	V1.0	03 July 2017
Summary CV for Chief Investigator (CI) [CI (Lawrence Impey) Research CV]	V1.0	03 July 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Non technical summary (OxGRIP)]	V1.0	03 July 2017

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Heather House

Tel: (01865) 572224

Email: heather.house@ouh.nhs.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	The study will involve analysis of routinely collected anonymised data only.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	An agreement will not be required as this is a non-commercial single site study where the single site is also the study sponsor.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	The study is not funded.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	The data analyst at the site will extract and anonymise the data. The research team will have access to non-identifiable data only.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There is one site-type. This is a non-commercial single site study where the single NHS site is also the study sponsor.

If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents

should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A key contact should be identified at the site to extract and anonymise the data for the research team. GCP training is <u>not</u> a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
No access arrangements are applicable as data will be collected and anonymised by staff from the site.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they <u>do not intend</u> to apply for inclusion on the NIHR CRN Portfolio.