A Low Cerebroplacental Ratio at 20–24 Weeks of Gestation Can Predict Reduced Fetal Size Later in Pregnancy or at Birth

Edgar Hernandez-Andrade^{a, b} Eli Maymon^{a, b} Offer Erez^{a, b} Homam Saker^{a, b}
Suchaya Luewan^{a–c} Maynor Garcia^{a, b} Hyunyoung Ahn^{a, b} Adi L. Tarca^{a, b}
Bogdan Donea^a Steven J. Korzeniewski^{a, b, d} Sonia S. Hassan^{a, b}
Roberto Romero^{a, d–f}

^aPerinatology Research Branch, NICHD/NIH/DHHS, Bethesda, MD and Detroit, MI, and ^bDepartment of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA; ^cDepartment of Obstetrics and Gynecology, Chiang Mai University, Chiang Mai, Thailand; ^dDepartment of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, ^eDepartment of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, and ^fCenter for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

Keywords

Adverse perinatal outcome · Birthweight · Doppler · Fetal growth restriction · Middle cerebral artery · Umbilical artery · Uterine arteries

Abstract

Aim: To determine whether Doppler evaluation at 20–24 weeks of gestation can predict reduced fetal size later in pregnancy or at birth. **Methods:** Fetal biometry and Doppler velocimetry were performed in 2,986 women with a singleton pregnancy at 20–24 weeks of gestation. Predictive performances of the umbilical artery pulsatility index (UA-PI) or the mean uterine artery pulsatility index (UtA-PI) >95th percentile, middle cerebral artery pulsatility index, or cerebroplacental ratio (CPR) <5th percentile for early small for gestational age (SGA; <34 weeks of gestation), late SGA (≥34 weeks of gestation), or SGA at birth (birthweight <10th percentile) were analyzed. **Results:** The prevalence of early SGA, late SGA, and SGA at birth was 1.1, 9.6, and 14.7%, respectively. A CPR <5th percentile had a positive likelihood ratio

(LR+) of 8.2 (95% confidence interval [CI] 5.7–12.0) for early SGA, a LR+ of 1.6 (95% CI 1.1–1.2) for late SGA, and a LR+ of 1.9 (95% CI 1.4–2.6) for SGA at birth. A UtA-PI >95th percentile was associated with late SGA and SGA at birth, while an UA-PI >95th percentile was associated with early SGA. Associations were higher in fetuses with an estimated fetal weight <10th percentile. **Conclusion:** Fetal biometry and Doppler evaluation at 20–24 weeks of gestation can predict early and late SGA as well as SGA at birth.

© 2017 S. Karger AG, Basel

Introduction

The potential of fetal growth can be affected by a hostile uterine environment that may be associated with a chronic reduction of the oxygen and nutrient supplies and will eventually be reflected in a low estimated fetal weight (EFW) [1–4]. The fetal hemodynamic response to these conditions is adaptive in nature and prioritizes an optimal supply of oxygen to the brain, heart, and adrenal

glands at the expense of muscle, bone, and fat tissue [5–12]. Therefore, fetal hemodynamic changes might be present prior to the reduced size of biometric parameters such as abdominal and head circumferences and femur length.

In fetuses already considered small for gestational age (SGA; EFW <10th percentile), an abnormal Doppler velocimetry of the umbilical artery (UA) or of the middle cerebral artery (MCA) has been associated with low pO₂ in umbilical cord blood [13], increased prevalence of cesarean deliveries for nonreassuring fetal status [14], low Apgar scores, admission to the neonatal intensive care unit, and long-term neurological complications [15–19]. Fetuses with an EFW <10th percentile and absent or reversed end-diastolic velocities in the UA have a 45–70% increased risk of perinatal death [20]. Therefore, Doppler evaluation of SGA fetuses can contribute to the characterization of the severity of the hypoxic insult, the identification of the optimal time for delivery, and reduction in the prevalence of perinatal mortality and morbidity [21–23].

Currently, however, Doppler studies are not recommended for fetuses with a normal EFW [24, 25]. The Cochrane Database of Systematic Reviews reported that there is still no clear evidence that a fetal Doppler examination of low-risk pregnant women can reduce the prevalence of fetal mortality/morbidity [25]. Similarly, fetal Doppler evaluation has not been recommended before the suggested time for normal or reduced fetal growth screening at 24 weeks of gestation [26]. Recently, De Paco et al. [27] explored the association between abnormal Doppler parameters obtained at 19–22 weeks of gestation and perinatal complications. The authors reported a 3.5 increment in the risk (95% confidence interval [CI] 1.7–7.1) of birthweight <5th percentile in the presence of an abnormal umbilical artery pulsatility index (UA-PI) >90th percentile. These results suggest that early Doppler fetal evaluation might contribute to the identification of fetuses at risk of reduced growth. In this study, we determined the diagnostic performance of fetal and uterine Doppler parameters at 20–24 weeks of gestation to detect fetuses who will show a reduction of size later in pregnancy or at birth.

Methods

Characteristics of the Study Population and Study Design

This cohort study was conducted at the Center for Advanced Obstetrical Care and Research (CAOCR), Perinatology Research Branch of the Eunice Kennedy Shriver National Institute of Child

Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS), Wayne State University School of Medicine, and Hutzel Women's Hospital, Detroit, MI, USA. All patients provided written informed consent for ultrasound examinations and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and by the Institutional Review Board of NICHD.

Our cohort included 2,986 women with a singleton pregnancy, consecutively enrolled before 17 weeks of gestation, who had routine prenatal follow-up at the CAOCR until delivery during the study period (2008–2012). The first ultrasound and Doppler evaluations for each patient obtained at 20–24 weeks of gestation were analyzed. Fetuses with congenital malformations or genetic abnormalities identified prenatally or at birth were excluded from the analysis.

Ultrasound and Doppler Measurements

Ultrasound and Doppler studies were performed using General Electric Voluson Expert and Voluson E8 (GE Healthcare, Milwaukee, WI, USA) ultrasound systems and 5- to 2-MHz probes. Gestational age was based on the last menstrual period and confirmed by crown-rump length measurement or by second-trimester ultrasound. EFW was calculated using the Hadlock formula [28] based on the combination of biparietal diameter, head circumference, abdominal circumference, and femur length. Normal EFW was considered to be ≥10th percentile and reduced EFW was considered to be <10th percentile for gestational age [29].

Doppler evaluation of the UA was performed in a free loop of the umbilical cord, the MCA in a cross-sectional view of the fetal head in the vascular circle of Willis at approximately 1 cm after its origin from the internal carotid artery, and the uterine arteries (UtA) in a parasagittal view of the uterus 1 cm above the virtual crossing with the iliac artery [30]. The mean uterine artery pulsatility index (UtA-PI) was estimated as the average of the left and right UtAs. The size of the Doppler sample gate was adjusted to cover the entire interrogated vessel. Doppler recordings were obtained in the absence of maternal or fetal movements with an angle of insonation as close as possible to 0°. Using a high-pass wall filter of 60 MHz, each vessel was sampled two to three times and the mean pulsatility index was calculated. For the UtA and UA, a pulsatility index value >95th percentile was considered abnormal [31]. The cerebroplacental ratio (CPR) was calculated as follows: middle cerebral artery pulsatility index (MCA-PI) / UA-PI; a CPR or MCA-PI <5th percentile for gestational age was considered abnormal [31]. All women were scheduled to have an ultrasound examination every 4 weeks until 28 weeks of gestation and every 2 weeks thereafter until delivery.

Clinical Outcomes

In this study, we aimed to explore the association between abnormal Doppler parameters at 20–24 weeks of gestation and small fetal size later in pregnancy or at birth. We also determined whether this association is modified by abnormal fetal size (EFW <10th percentile) at 20–24 weeks of gestation. All fetuses were followed until delivery and the clinical outcomes were defined as follows: (1) early SGA as an EFW <10th percentile at <34 weeks of gestation [32], (2) late SGA as an EFW <10th percentile at ≥34 weeks of gestation [33, 34], and (3) SGA at birth as birthweight <10th percentile [35]. The information provided by Doppler parameters at 20–24 weeks of gestation was not used for clinical management.

Table 1. Clinical characteristics and outcomes of the study groups

	Early SGA (<i>n</i> = 35)	Late SGA (<i>n</i> = 288)	SGA at birth (<i>n</i> = 439)	No prenatal SGA or SGA at birth (<i>n</i> = 2,387)
Maternal age, years	23 (20–31)	23 (20–26)	25 (22–29)	23 (20–27)
African-American	33 (94.3%)	275 (95.5%)	414 (94.3%)	2,176 (91.2%)
Nulliparity	9 (25.7%)	77 (26.7%)	142 (32.3%)	570 (23.9%)
BMI at beginning of pregnancy	29 (25–33)	26 (22–30)	25 (21–30)	27 (23–33)
Smoking	7 (20.0%)	67 (23.3%)	123 (28.0%)	416 (17.4%)
MABP at diagnosis, mm Hg	112.6 (100–131)	95.6 (89–104)	96.3 (89–108)	96 (87–104)
Preeclampsia	6 (17.1%)	18 (6.3%)	54 (12.3%)	127 (5.3%)
Fetal death	4 (11.4%)	0	–	8 (0.3%)
GA at delivery, weeks	33 (27–38)	38 (37–39)	38.6 (37.1–39.4)	39.1 (38–40)
Cesarean section	21 (60.0%)	81 (28.1%)	144 (32.8%)	659 (27.6%)
Birthweight, g	1,305 (678–2,761)	2,705 (2,395–2,970)	2,521 (2,257–2,702)	3,270 (2,995–3,580)
Male sex	21 (60.0%)	141 (49.0%)	248 (56.5%)	1,086 (45.5%)
SGA	22 (62.9%)	152 (52.8%)	–	–
Low pH (<7.05)	2 (5.7%)	5 (1.7%)	17 (3.9%)	31 (1.3%)
Low Apgar score (<6)	6 (17.1%)	4 (1.4%)	20 (4.6%)	61 (2.6%)
Perinatal death	6 (17.1%)	0	2 (0.5%) ^a	22 (0.9%)
Intraventricular hemorrhage	1 (2.9%)	3 (1.0%)	8 (1.8%) ^b	44 (1.8%)
Necrotizing enterocolitis	5 (14.3%)	1 (0.3%)	4 (0.9%) ^c	31 (1.3%)

Values are presented as *n* (%) or median (interquartile range). BMI, body mass index; GA, gestational age; MABP, mean arterial blood pressure; SGA, small for gestational age. ^a Neonatal. ^b One with early SGA and two with late SGA. ^c Three with early SGA.

Statistical Analysis

The diagnostic performance of all Doppler parameters for early and late SGA as well as for SGA at birth was estimated. Relative risk (RR) and odds ratios (OR) were calculated and the analysis accounted for potential confounders such as maternal age, gestational age at examination, mean arterial blood pressure, smoking, parity, alcohol and drug use, and body mass index. Differences in the CPR at 20–24 weeks in fetuses who were later diagnosed with early or late SGA were evaluated using the Wilcoxon rank sum test. A *p* value <0.05 was considered statistically significant. Analyses were performed using SPSS® Version 19 (IBM Corp., Armonk, NY, USA) and MedCalc® 9.0.1.0 (MedCalc Software bvba, Ostend, Belgium) statistical software. RRs were obtained by a Poisson regression model with robust estimation of the variance using the “geepack” package under the R statistical environment (www.r-project.org). The primary measure used to rank the Doppler parameters based on their prediction performance was the positive likelihood ratio (LR+).

Results

This study included 2,986 patients; the success rate for obtaining Doppler parameters was as follows: UA-PI in 2,829 fetuses (94.7%; variation among individual measurements: median 4.9%, interquartile range [IQR] 2.7–10%); MCA-PI and CPR in 2,505 fetuses (83.6%; variation among individual measurements: median 3.8%, IQR,

2.4–6.7%); and mean UtA-PI in 2,848 women (95.3%; variation among individual measurements: median 13%, IQR 3.5–15.7%). The prevalence of early SGA was 1.1% (*n* = 35/2,986), of late SGA 9.6% (*n* = 288/2,986), and of SGA at birth 14.7% (*n* = 439/2,986). The demographic characteristics of the study population according to outcome groups are described in Table 1.

The study cohort was stratified according to the EFW calculated during the first ultrasound examination at 20–24 weeks; 2,800 women (93.8%) had fetuses with an EFW ≥10th percentile, and 186 (6.2%) had fetuses with an EFW <10th percentile. In fetuses with an EFW ≥10th percentile, 18 (0.6%) had early SGA and 231 (8.2%) had late SGA, while among those with an EFW <10th percentile, 17 (9.1%) had early SGA and 57 (30.6%) had late SGA. The increase in the percentage of early and late SGA among fetuses with an EFW <10th percentile compared to those with an EFW ≥10th percentile was significant (*p* < 0.001 for both) (Fig. 1). There were 13 fetal deaths (Table 2): 4 fetuses with an EFW <10th percentile (4/186, 2.1%) and 9 fetuses with an EFW ≥10th percentile (9/2,800, 0.3%). The rate of SGA at birth in fetuses with an EFW <10th percentile was higher (74/186, 39.8%) than in those with an EFW ≥10th percentile (365/2,800, 13.1%) (*p* < 0.0001). Table 3 shows the clinical characteristics and

Fig. 1. Outcomes for 2,986 fetuses evaluated at 20–24 weeks and classified according to estimated fetal weight (EFW) and further development of early or late small-for-gestational-age (SGA) fetuses and SGA newborns. FGR, fetal growth restriction; IUFD, intrauterine fetal death.

Table 2. Clinical characteristics of patients with fetal demise (*n* = 13)

EFW <10th percentile at 20–24 weeks	4 (30.7%)
Age, years	21 (20–28)
Body mass index	30 (24–34)
Mean arterial blood pressure, mm Hg	111 (96–125)
Smoking	1 (7.6%)
Preeclampsia	2 (15.3%)
Chronic hypertension	3 (23.1%)
Gestational diabetes mellitus	1 (7.6%)
Gestational age at delivery, weeks	27 (25–30)
Birthweight, g	752 (373–1,335)
UA-PI >95th percentile	4 (30.7%)
Cerebroplacental ratio <5th percentile	4 (30.7%)
Mean UtA-PI >95th percentile	3 (23.1%)

Values are presented as *n* (%) or median (interquartile range). EFW, estimated fetal weight; UA-PI, umbilical artery pulsatility index; UtA-PI, uterine artery pulsatility index.

Fig. 2. Distribution of the cerebroplacental ratio (CPR) values at 20–24 weeks of gestation for fetuses who later in pregnancy showed early small for gestational age (SGA; estimated fetal weight <10th percentile) <34 weeks of gestation, late SGA ≥34 weeks of gestation, or SGA at birth (birthweight <10th percentile) as well as for fetuses of normal size during pregnancy and at birth. * *p* < 0.05 in comparison to any other group.

perinatal outcomes of fetuses with an EFW <10th or ≥10th percentile at 20–24 weeks of gestation.

The median CPR at 20–24 weeks of gestation was significantly lower in fetuses who later developed early SGA as compared to those presenting late SGA, SGA at birth, or with normal fetal size and birthweight (all *p* < 0.05). No differences in the median CPR were observed among fetuses later presenting late SGA or SGA at birth or fetuses presenting with normal size during pregnancy and at birth (Fig. 2).

Doppler Parameters at 20–24 Weeks of Gestation and in Early SGA Fetuses

Among all Doppler parameters, the MCA-PI showed the lowest LR+ for the association between early or late SGA and SGA at birth. The diagnostic performance of

Doppler parameters for the subsequent development of early SGA was as follows (Table 4): For the complete study group: (1) CPR <5th percentile: sensitivity 54%, false-positive rate (FPR) 7%, positive predictive value (PPV) 9.1%, negative predictive value (NPV) 99.4%, LR+ 8.2 (95% CI 5.7–12.0), and RR 15.4 (95% CI 7.7–30.7); (2) UA-PI >95th percentile: sensitivity 60.6%, FPR 8%, PPV 8.3%, NPV 99.5%, LR+ 7.6 (95% CI 5.6–10.0), and RR 16.4 (95% CI 8.2–32.5); and (3) UtA-PI >95th percentile: sensitivity 43.3%, FPR 9%, PPV 4.8%, NPV 99.3%, LR+ 4.7 (95% CI

Table 3. Clinical characteristics and outcomes of the study group according to estimated fetal weight at 20–24 weeks of gestation

	EFW <10th percentile (n = 186)	EFW ≥10 percentile (n = 2,800)	p value
Low Apgar score	7 (3.7%)	70 (2.5%)	0.41
Perinatal death	5 (2.6%) ^a	25 (0.9%)	0.03
pH <7.05	0	44 (1.5%)	0.11
Intraventricular hemorrhage	5 (2.6%)	48 (1.7%)	0.37
Necrotizing enterocolitis	5 (2.6%) ^a	33 (1.1%)	0.08
Preeclampsia	13 (6.9%)	167 (5.9%)	0.9
African-American	163 (87.6%)	2,565 (91.6%)	0.9
Female sex	100 (53.7%)	1,299 (46.4%)	0.9
Fetal death	4 (2.1%) ^a	9 (0.3%)	0.006
Birthweight, g	2,532 (1,398–3,080) ^a	3,180 (2,822–3,510)	<0.0001
Gestational age at delivery, weeks	37 (33–40) ^a	39 (37–40)	0.005
Cesarean section	54 (29.0%)	782 (27.9%)	1.0

Values are presented as n (%) or median (interquartile range). EFW, estimated fetal weight. ^ap < 0.05.

Table 4. Associations of abnormal Doppler parameters at 20–24 weeks of gestation and early small for gestational age fetuses (estimated fetal weight <10th percentile before 34 weeks of gestation)

Doppler	SN, %	SP, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	RR (95% CI)
<i>All study groups (prevalence n = 35; 1.2%)</i>									
CPR	54.0	93.0	9.1	99.4	8.2 (5.7–12.0)	0.5 (0.3–0.7)	16.8 (8.1–34.7)	13.9 (6.5–24.5)	15.4 (7.7–30.7)
UtA-PI	43.3	91.0	4.8	99.3	4.7 (3.1–7.2)	0.6 (0.5–0.8)	7.6 (3.6–15.7)	6.5 (3.6–10.7)	7.3 (3.6–14.8)
CPR or UtA-PI	74.1	83.9	5.3	99.6	4.6 (3.6–5.8)	0.3 (0.2–0.6)	15 (6.7–33.8)	11.7 (5.1–27.0)	14.2 (6.4–31.7)
UA-PI	60.6	92.0	8.3	99.5	7.6 (5.6–10.0)	0.4 (0.3–0.7)	17.7 (8.7–36.2)	24.5 (13.6–45.4)	16.4 (8.2–32.5)
MCA-PI	27.3	88.3	2.9	99.0	2.3 (1.3–4.1)	0.8 (0.7–1.0)	2.8 (1.3–6.16)	2.5 (1.4–4.5)	2.8 (1.3–5.9)
<i>EFW <10th percentile (prevalence n = 17; 9.1%)</i>									
CPR	69.2	93.2	47.4	97.2	10 (5.1–21)	0.3 (0.2–0.8)	31.1 (8.1–118.7)	41.6 (8.2–327.7)	16.8 (5.7–49.3)
UtA-PI	28.6	88.4	17.4	93.5	2.5 (0.9–6.3)	0.8 (0.6–1.1)	3.1 (0.9–10.1)	2.3 (0.4–10)	2.7 (0.9–7.90)
CPR or UtA-PI	84.6	81.7	28.9	98.4	4.6 (3.0–7.0)	0.2 (0.1–0.7)	24.6 (5.1–117.6)	20.3 (3.9–104.6)	17.8 (4.1–76.8)
UA-PI	86.7	89.0	41.9	97.6	7.9 (4.9–13)	0.2 (0.04–0.5)	52.3 (10.9–251)	91.6 (14.8–1,239.8)	30.8 (7.3–129.7)
MCA-PI	20.0	90.1	16.7	91.9	2.0 (0.7–6.2)	0.9 (0.7–1.2)	2.3 (0.6–8.9)	1.9 (0.3–8.2)	2.1 (0.6–6.6)
<i>EFW ≥10th percentile (prevalence n = 18; 0.6%)</i>									
CPR	44.4	93.3	4.8	99.5	6.6 (3.9–11)	0.6 (0.4–0.9)	11.1 (4.3–28.4)	9.9 (4.4–22)	10.6 (4.2–26.5)
UtA-PI	56.3	91.0	3.6	99.7	6.2 (4–9.8)	0.5 (0.3–0.8)	12.9 (4.8–35.2)	11 (5.3–26)	12.5 (4.7–33.9)
CPR or UtA-PI	66.7	84.1	3.0	99.7	4.2 (3.0–5.9)	0.4 (0.2–0.8)	10.5 (3.9–28.3)	8.0 (2.8–22.4)	10.3 (3.9–27.2)
UA-PI	38.9	92.2	3.3	99.5	5.0 (2.3–9.1)	0.7 (0.5–0.9)	7.5 (2.9–19.7)	13.3 (6.3–31.7)	7.3 (2.9–18.7)
MCA-PI	33.3	88.2	2.1	99.4	2.8 (1.5–5.5)	0.8 (0.6–1.1)	3.7 (1.4–10.1)	3.3 (1.5–6.7)	3.7 (1.4–9.7)

ORs adjusted for maternal age, race, nulliparity, smoking, alcohol use, drug use, pre-pregnancy body mass index, and mean arterial blood pressure. CI, confidence interval; CPR, cerebroplacental ratio <5th percentile; EFW, estimated fetal weight; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MCA-PI, middle cerebral artery pulsatility index <5th percentile; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RR, relative risk; SN, sensitivity; SP, specificity; UA-PI, umbilical artery pulsatility index >95th percentile; UtA-PI, uterine artery pulsatility index >95th percentile.

3.1–7.2), and RR 7.3 (95% CI 3.6–14.8). For fetuses with an EFW <10th percentile: (1) CPR <5th percentile: sensitivity 69.2%, FPR 6.8%, PPV 47.4%, NPV 97.2%, LR+ 10.0 (95% CI 5.1–21), and RR 16.8 (95% CI 5.7–49.3); and (2) UA-PI >95th percentile: sensitivity 86.7%, FPR 11%, PPV

41.9%, NPV 97.6%, LR+ 7.9 (95% CI 4.9–13.0), and RR 30.8 (95% CI 7.3–129.7). The diagnostic performance of Doppler parameters for early SGA in fetuses with an EFW ≥10 percentile at 20–24 weeks of gestation was similar to that observed in the entire study population.

Table 5. Diagnostic performance, likelihood ratios, and associations of Doppler parameters at 20–24 weeks of gestation and late small for gestational age fetuses (estimated fetal weight <10th percentile at ≥34 weeks of gestation)

Doppler	SN, %	SP, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	RR (95% CI)
<i>All (prevalence n = 288; 10.2%)</i>									
CPR	10.8	93.1	14.1	90.9	1.6 (1.1–2.3)	0.9 (0.9–1.0)	1.6 (1.1–2.5)	1.6 (1–2.5)	1.5 (1.1–2.2)
UtA-PI	14.5	91.0	14.8	90.8	1.6 (1.2–2.2)	0.9 (0.9–0.99)	1.7 (1.2–2.5)	1.7 (1.2–2.5)	1.6 (1.2–2.2)
CPR or UtA-PI	24.8	82.3	14.1	91.2	1.5 (1.2–1.9)	0.9 (0.8–0.9)	1.7 (1.3–2.4)	1.7 (1.3–2.4)	1.6 (1.2–2.1)
UA-PI	9.9	91.6	11.2	90.5	1.2 (0.8–1.7)	0.9 (0.9–1.1)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.2 (0.8–1.7)
MCA-PI	14.1	88.4	11.3	90.7	1.2 (0.9–1.7)	0.9 (0.9–1.0)	1.2 (0.9–1.8)	1.2 (0.8–1.8)	1.2 (0.9–1.7)
<i>EFW <10th percentile (prevalence n = 57; 30.6%)</i>									
CPR	7.0	86.4	15.8	71.8	0.5 (0.2–1.7)	1.1 (0.9–1.2)	0.5 (0.1–1.7)	0.4 (0.1–1.5)	0.6 (0.2–1.6)
UtA-PI	12.0	86.7	26.1	71.6	0.9 (0.4–2.2)	1.0 (0.9–1.2)	0.9 (0.4–2.4)	0.8 (0.3–2.4)	0.9 (0.4–1.9)
CPR or UtA-PI	20.1	75.4	23.7	72.4	0.8 (0.4–1.7)	1.0 (0.9–1.3)	0.8 (0.4–1.9)	0.8 (0.3–2.1)	0.9 (0.4–1.6)
UA-PI	6.0	78.1	9.7	68.0	0.3 (0.1–1.4)	1.2 (0.1–1.4)	0.2 (0.1–0.8)	0.2 (0–0.6)	0.3 (0.1–0.9)
MCA-PI	11.6	89.4	27.8	74.3	1.1 (0.4–2.9)	1.0 (0.8–1.1)	1.1 (0.4–3.2)	1.1 (0.3–3.2)	1.0 (0.5–2.4)
<i>EFW >10th percentile (prevalence n = 231; 8.2%)</i>									
CPR	11.7	93.4	13.9	92.1	1.8 (1.2–2.7)	0.9 (0.9–1.0)	1.8 (1.1–2.9)	1.9 (1.1–2.5)	1.8 (1.1–2.6)
UtA-PI	15.0	91.2	13.7	92.1	1.7 (1.2–2.4)	0.9 (0.9–1.0)	1.8 (1.2–2.7)	1.9 (1.2–2.8)	1.7 (1.2–2.4)
CPR or UtA-PI	25.6	84.5	13.4	92.3	1.6 (1.3–2.1)	0.9 (0.8–1.0)	1.9 (1.4–2.6)	1.9 (1.4–2.7)	1.7 (1.3–2.3)
UA-PI	10.8	92.3	11.4	91.8	1.4 (0.9–2.1)	1.0 (0.9–1.0)	1.4 (0.9–2.3)	1.4 (1–2.3)	1.4 (0.9–2.0)
MCA-PI	14.6	88.3	10.3	91.8	1.2 (0.9–1.8)	1.0 (0.9–1.0)	1.3 (0.9–1.9)	1.3 (0.8–1.9)	1.3 (0.8–1.8)

ORs adjusted for maternal age, race, nulliparity, smoking, alcohol use, drug use, pre-pregnancy body mass index, and mean arterial blood pressure. CI, confidence interval; CPR, cerebroplacental ratio <5th percentile; EFW, estimated fetal weight; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MCA-PI, middle cerebral artery pulsatility index <5th percentile; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RR, relative risk; SN, sensitivity; SP, specificity; UA-PI, umbilical artery pulsatility index >95th percentile; UtA-PI, uterine artery pulsatility index >95th percentile.

Table 6. Diagnostic performance, likelihood ratios, and associations of Doppler parameters at 20–24 weeks of gestation and small for gestational age at birth (birthweight <10th percentile)

Doppler	SN, %	SP, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	RR (95% CI)
<i>All (prevalence n = 439; 15.6%)</i>									
CPR	12.1	93.5	23.8	86.3	1.9 (1.4–2.6)	0.9 (0.9–1.0)	2.0 (1.4–2.8)	1.8 (1.2–2.6)	1.7 (1.3–2.3)
UtA-PI	21.0	92.5	32.5	87.2	2.8 (2.2–3.5)	0.9 (0.8–0.9)	3.3 (2.4–4.3)	3.3 (2.4–4.4)	2.5 (2.1–3.1)
CPR or UtA-PI	30.9	85.7	27.3	87.7	2.2 (1.8–2.6)	0.8 (0.7–0.9)	2.7 (2.1–3.5)	2.6 (2.0–3.2)	2.2 (1.8–2.7)
UA-PI	13.3	92.2	22.8	86.0	1.7 (1.3–2.3)	0.9 (0.9–0.98)	1.8 (1.3–2.5)	1.8 (1.3–2.5)	1.6 (1.3–2.1)
MCA-PI	11.7	88.1	14.2	85.5	1.0 (0.7–1.3)	1.0 (0.96–1.04)	0.9 (0.7–1.4)	0.9 (0.6–1.2)	0.9 (0.7–1.3)
<i>EFW <10th percentile (prevalence n = 74; 39.8%)</i>									
CPR	20.6	93.9	68.4	64.7	3.4 (1.4–8.4)	0.8 (0.7–1.0)	4.0 (1.4–11.1)	3.0 (1–10.1)	1.9 (1.0–3.5)
UtA-PI	22.5	93.5	69.6	64.5	3.4 (1.5–7.9)	0.8 (0.7–1.0)	4.2 (1.6–10.7)	4.0 (1.4–12.9)	2.0 (1.4–2.7)
CPR or UtA-PI	41.2	87.7	68.4	69.9	3.3 (1.8–6.2)	0.7 (0.5–0.8)	5.0 (2.3–11.0)	4.5 (1.9–10.6)	2.2 (1.6–3.2)
UA-PI	22.5	86.0	51.6	62.6	1.6 (0.8–3.0)	0.9 (0.8–1.0)	1.8 (0.8–3.9)	1.4 (0.6–3.4)	1.4 (0.9–2.1)
MCA-PI	15.6	92.2	55.6	63.5	2.0 (0.8–4.8)	0.9 (0.8–1.0)	2.2 (0.8–5.8)	2.2 (0.7–7)	1.5 (0.9–2.4)
<i>EFW >10th percentile (prevalence n = 365; 13.1%)</i>									
CPR	10.3	93.5	18.7	87.8	1.6 (1.1–2.3)	1.0 (0.9–1.0)	1.6 (1.1–2.5)	1.5 (1–2.3)	1.5 (1.1–2.1)
UtA-PI	20.7	92.4	29.0	88.6	2.7 (2.1–3.5)	0.9 (0.8–0.9)	3.2 (2.3–4.3)	3.2 (2.3–4.4)	2.6 (2.0–3.2)
CPR or UtA-PI	29.0	85.1	23.3	88.8	2.0 (1.6–2.5)	0.8 (0.8–0.9)	2.4 (1.8–3.2)	2.3 (1.7–3.1)	2.0 (1.7–2.6)
UA-PI	11.4	92.5	18.6	87.5	1.5 (1.1–2.1)	1.0 (0.9–1.0)	1.6 (1.1–2.3)	1.6 (1.1–2.4)	1.5 (1.1–2.0)
MCA-PI	10.9	87.9	11.7	87.1	1.0 (0.7–1.3)	1.0 (1.0–1.0)	0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.9 (0.6–1.2)

ORs adjusted for maternal age, race, nulliparity, smoking, alcohol use, drug use, pre-pregnancy body mass index, and mean arterial blood pressure. CI, confidence interval; CPR, cerebroplacental ratio <5th percentile; EFW, estimated fetal weight; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MCA-PI, middle cerebral artery pulsatility index <5th percentile; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RR, relative risk; SN, sensitivity; SP, specificity; UA-PI, umbilical artery pulsatility index >95th percentile; UtA-PI, uterine artery pulsatility index >95th percentile.

Doppler Parameters at 20–24 Weeks of Gestation and in Late SGA Fetuses

The diagnostic performance of Doppler parameters for the subsequent development of late SGA was as follows (Table 5): For the complete study group: (1) CPR <5th percentile: sensitivity 10.8%, FPR 6.9%, PPV 14.1%, NPV 90.9%, LR+ 1.6 (95% CI 1.1–2.3), and RR 1.5 (95% CI 1.2–2.2); (2) UtA-PI >95th percentile: sensitivity 14.5%, FPR 9%, PPV 14.8%, NPV 90.8%, LR+ 1.6 (95% CI 1.1–2.2), and RR 1.6 (95% CI 1.2–2.2); and (3) UA-PI >95th percentile: sensitivity 9.9%, FPR 8.4%, PPV 11.2%, NPV 90.5%, LR+ 1.2 (95% CI 0.8–1.7), and RR 1.2 (95% CI 0.8–1.7). For fetuses with an EFW <10th percentile: (1) CPR <5th percentile: sensitivity 7.0%, FPR 13.6%, PPV 15.8%, NPV 71.8%, LR+ 0.5 (95% CI 0.2–1.7), and RR 0.6 (95% CI 0.2–1.6); and (2) UtA-PI >95th percentile: sensitivity 12.0%, FPR 13.3%, PPV 26.1%, NPV 71.6%, LR+ 0.9 (95% CI 0.4–2.2), and RR 0.9 (95% CI 0.4–1.9). The diagnostic performance of Doppler parameters for late SGA in fetuses with an EFW ≥ 10 percentile at 20–24 weeks of gestation did not significantly vary from that observed for the entire study population.

Doppler Parameters at 20–24 Weeks of Gestation and in SGA at Birth

The diagnostic performance of Doppler parameters for SGA at birth was as follows (Table 6): For the complete study group: (1) CPR <5th percentile: sensitivity 12.1%, FPR 6.5%, PPV 23.8%, NPV 86.3%, LR+ 1.9 (95% CI 1.4–2.6), and RR 1.7 (95% CI 1.3–2.3); (2) UtA-PI >95th percentile: sensitivity 21.0%, FPR 7.5%, PPV 32.5%, NPV 87.2%, LR+ 2.8 (95% CI 2.2–3.5), and RR 2.5 (95% CI 2.1–3.1); and (3) UA-PI >95th percentile: sensitivity 13.3%, FPR 7.8%, PPV 22.8%, NPV 86%, LR+ 1.7 (95% CI 1.3–2.3), and RR 1.6 (95% CI 1.3–3.5). For fetuses with an EFW <10th percentile: (1) CPR <5th percentile: sensitivity 20.6%, FPR 6.1%, PPV 68.4%, NPV 64.7%, LR+ 3.4 (95% CI 1.4–8.4), and RR 1.9 (95% CI 1.3–2.8); and (2) UtA-PI >95th percentile: sensitivity 22.5%, FPR 6.5%, PPV 69.6%, NPV 64.5%, LR+ 3.4 (95% CI 1.5–7.9), and RR 2.0 (95% CI 1.4–2.7). The diagnostic performance of Doppler parameters for SGA at birth in fetuses with an EFW ≥ 10 percentile at 20–24 weeks of gestation did not significantly vary from that observed for the entire study population.

Figure 3 shows the RRs (95% CI) of early SGA (upper panel) and late SGA (lower panel) for fetuses at 20–24 weeks of gestation with a CPR <5th percentile and an EFW less than a given cutoff. At any EFW percentile cut-

Fig. 3. Relative risks with 95% confidence intervals (y axis) for early small for gestational age (SGA) (<34 weeks of gestation; upper panel) or late SGA (≥ 34 weeks of gestation; lower panel) for fetuses with a cerebroplacental ratio <5th percentile at 20–24 weeks of gestation and an estimated fetal weight (EFW) less than a given cutoff (x axis).

off, a reduced CPR significantly increased the risk of early SGA. The EFW cutoff at which the area under the receiver operating characteristics curve was highest (Fig. 4) was EFW 7th percentile and corresponded to a sensitivity of 73%, a specificity of 94%, and a LR+ of 12.16 for identification of early SGA.

Predictive Performance of a CPR <5th Percentile or a UtA-PI >95th Percentile

The sensitivity of this combined Doppler evaluation for the detection of early fetal growth restriction increased to 74.1% (from 54%) and for late fetal growth restriction to 24.8% (from 10.8%) compared to a CPR <5th percentile alone, whereas the specificity was lower (83.9 and 84.10%, respectively, compared to 93% for both with a CPR <5th percentile alone), thus resulting in lower positive LR. Similar findings were observed for SGA at birth, where sensitivity increased from 21.0 to 30.9%, but with lower specificity (85.7 vs. 92.5%, respectively) when compared to a UtA-PI >95th percentile alone, resulting in similar positive LR.

Fig. 4. The receiver operating characteristics curve shows early fetal growth restriction for fetuses with an abnormal cerebroplacental ratio (<5th percentile) and an estimated fetal weight <7th percentile.

Discussion

The principal findings of this study are as follows: (1) a CPR <5th percentile at 20–24 weeks of gestation can detect fetuses who will show early SGA, late SGA, and SGA at birth; (2) a UtA-PI and an UA-PI >95th percentile were also associated with the subsequent development of early SGA, late SGA, and SGA at birth; (3) a CPR <5th percentile at 20–24 weeks of gestation had a LR+ of 10 for the detection of early SGA; (4) at an EFW corresponding to the 7th percentile at 20–24 weeks of gestation, a CPR <5th percentile had an OR of 39.47 and a LR+ of 12.16 for the identification of early SGA. These results suggest that the ratio of the hemodynamic changes in the fetal-placental circulation and in the fetal brain at 20–24 weeks of gestation can be a sensitive tool for the early identification of women at risk of the subsequent development of early SGA.

Early Evaluation of Doppler Parameters in the Assessment of Fetal Growth

Fetal Doppler velocimetry is usually performed after 24 weeks of gestation as a complementary method to the nonstress test and the fetal biophysical profile for the clinical management of SGA fetuses [26], while the UtAs are

the vascular parameters most frequently evaluated at <24 weeks of gestation to identify fetuses at risk of reduced fetal growth later in pregnancy [36]. In accordance with previous studies [37–40], we found that an increased mean UtA-PI at <24 weeks of gestation was mainly associated with late SGA and with SGA at birth. Recent findings suggest that an interrogation of fetal vessels at 20–24 weeks of gestation may also play a role in the identification of the subsequent development of SGA. De Paco et al. [27] conducted a large study addressing the performance of the UA during the second-trimester ultrasound scan. The authors measured the UA-PI in 4,565 fetuses at 19–22 weeks of gestation and reported that an UA-PI >90th percentile was significantly associated with the delivery of an SGA neonate (birthweight <5th and <10th percentiles) with a LR of 1.7 (95% CI 1.2–2.4) for birthweight <10th percentile. In the current study, we demonstrated a similar performance of the UA-PI >90th percentile for the identification of women who subsequently delivered an SGA neonate (LR+ 1.7 [95% CI 1.3–2.3]). A novel finding of our study indicates that an evaluation of the CPR at 20–24 weeks of gestation can detect fetuses who will show reduced size later in pregnancy. Indeed, a CPR <5th percentile in fetuses with an EFW <10th percentile is also associated with a significantly higher risk of early SGA (LR+ 10.0 [95% CI 5.1–21.0]). This early SGA group should be considered a high-risk group; according to our data, these patients had an 11.4% prevalence of fetal mortality. These pregnancies might benefit from close clinical surveillance to identify or prevent contributing factors that can increase the risk of perinatal mortality and morbidity [41–46].

Doppler Velocimetry and Low EFW

The study of the fetal circulation using Doppler ultrasound is mainly confined to the assessment of fetuses with reduced size/growth. The rationale for this approach is that Doppler velocimetry can characterize the fetal hemodynamic deterioration and contribute to the clinical management of these fetuses [47–49]. The UA remains the main Doppler parameter for fetal assessment; recent studies have shown that the measurement of the CPR improved the early identification of fetuses at a higher risk of adverse outcome [50–52]. Based on these findings, Figueras and Gratacos [53] proposed an alternative definition for late SGA that includes an EFW <10th percentile, a decreased CPR, or an increased mean UtA-PI. These authors reported that the combination of an EFW <10th percentile and abnormal Doppler parameters can identify more fetuses at risk of perinatal complications

such as intrapartum fetal distress and neonatal acidosis. In the sequence of fetal Doppler deterioration, reduced diastolic velocity in the UA can be considered a manifestation of late hemodynamic deterioration. While the CPR represents a balance between the placental resistance to flow and the brain's compensatory mechanism associated with fetal growth restriction, it has been proposed that this parameter may be more sensitive to subtle fetal hemodynamic changes and that an abnormal CPR value may identify a fetus at risk of abnormal growth and perinatal complications earlier in gestation compared to a Doppler of the UA [52]. Indeed, we supported this hypothesis, presenting a novel finding that a reduced CPR at 20–24 weeks of gestation is significantly associated with an increased risk of early SGA.

The CPR as a Manifestation of Reduced Fetal Size

The importance of the CPR as a hemodynamic manifestation of blood flow redistribution in fetuses who are at the early stages of reduced fetal size was reported by Morales-Rosello et al. [54]. The authors demonstrated in fetuses with normal EFW that the closer the EFW is to the 10th percentile, the lower the CPR. They evaluated 11,576 pregnant women and reported that the CPR 5th percentile corresponded to 0.6765 multiples of the median (MoM), and their results indicated that 6.0% of fetuses with an EFW between the 75th and 90th percentiles, 7.9% of fetuses with an EFW between the 25th and 50th percentiles, and 11.6% of fetuses with an EFW between the 10th and 25th percentiles all had a CPR ≤ 0.6765 MoM. The authors also showed that fetuses with an EFW < 10 th percentile had a 22.2% prevalence of a CPR < 5 th percentile suggesting that, although the fetuses had not reached the threshold of SGA, a low CPR (< 0.676 MoM) might be used as a surrogate of reduced size and as a potential predictor of neonatal neurodevelopmental impairment. This observation was supported by Prior et al. [55] who conducted a prospective observational study of 775 women with a low-risk term pregnancy who had a Doppler examination within 72 h of delivery. When the fetuses were divided into two groups according to the CPR measurement, using the cutoff value suggested by Morales-Rosello et al. [54] (< 0.6765 MoM or ≥ 0.6765 MoM), the women with a CPR below the cutoff had a significantly increased risk of cesarean delivery due to fetal distress. Khalil et al. [56] reported that a low CPR, independent of the EFW, was associated with an increased prevalence of stillbirth and perinatal mortality [57]. Similar results were reported by Triunfo et al. [58] who showed that a low CPR in the third trimester of pregnancy had a higher association

with adverse perinatal outcomes such as nonreassuring fetal status requiring emergency cesarean delivery, a 5-min Apgar score < 7 , or neonatal metabolic acidosis at birth (UA pH ≤ 7.15 and base excess > 12 mEq/L) compared to EFW. These observations led to the evaluation of the CPR as a screening tool for pregnant women during the third trimester of pregnancy to identify fetuses at risk of late SGA [59, 60], stillbirth, low pH in the umbilical cord, low Apgar scores, cesarean delivery for fetal distress, and admission to the neonatal intensive care unit [60–62].

Additionally, an abnormal CPR for SGA fetuses is associated with a short interval to delivery [63], increased prevalence of abnormal fetal heart rate monitoring during labor [64], composite adverse perinatal outcome [65], and placental lesions associated with maternal underperfusion (e.g., muscularized arteries, atherosclerosis, and mural hypertrophy) [66]. The Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction (PORTO) study explored the utilization of the CPR for 881 growth-restricted fetuses at 33 weeks of gestation and reported that a CPR < 1 was associated with an increased rate of perinatal complications (18%) versus only 2% for fetuses with a CPR > 1 (OR 11.7 [95% CI 6.0–22.9]) [67]. The same group reported that, in a considerable proportion of cases, the CPR can improve in subsequent examinations, thus reducing the perinatal risks. From a total of 87 fetuses with a CPR < 1 , 45 (52%) remained abnormal in subsequent ultrasound scans, and 10 (22%) had an adverse perinatal outcome, whereas of the 42 (48%) fetuses who had an improved CPR, only 2 (5%) had an abnormal perinatal outcome [68]. Collectively, this evidence suggests that the CPR might be an important tool in the estimation of perinatal risks for normal and complicated pregnancies.

Our study is the first to test the utilization of the CPR at 20–24 weeks of gestation in the risk assessment of subsequent fetal growth restriction. We identified already at the early stages of pregnancy (especially in fetuses with reduced size) patients who will subsequently have early SGA (< 34 weeks of gestation), late SGA, and SGA at birth. These findings are novel and suggest that hemodynamic changes in fetuses with affected growth can be identified in the second trimester of pregnancy.

Clinical Implications

Maternal-fetal Doppler evaluation conducted at 20–24 weeks of gestation is not universally accepted; however, available reports show that a mean UtA-PI > 95 th percentile at this gestational age can identify women at risk of

preeclampsia and SGA [39, 69]. The evaluation of two additional fetal Doppler parameters – the UA and the MCA – in combination with EFW can improve the identification of fetuses at a higher risk of reduced size later in pregnancy. The presence of abnormal Doppler parameters at this gestational age might increase the frequency of clinical visits, but no decisions concerning delivery will be made. Fetuses with a reduced CPR might benefit from closer clinical surveillance, thus allowing the identification of the early stages of fetal decompensation for the purpose of steroid administration and the decision on the optimal time for delivery. Fetal and maternal Doppler parameters have the potential to improve the clinical information provided by the fetal biometric evaluation [70].

The strengths of our study are that (1) all fetuses were evaluated using the same protocol for biometric and Doppler measurements, and (2) clinical management and deliveries were performed at the CAOCR and followed the same standard guidelines. The information derived from the Doppler parameters at 20–24 weeks of gestation was not used for clinical management. Our study included a majority of African-American women, most of them parous, with a prevalence of 5–7% for preeclampsia. The diagnostic performance of Doppler parameters at 20–24 weeks of gestation to predict fetal growth restriction and SGA at birth might differ in other populations. Technical aspects and time constraints were the main reasons why not all Doppler measurement parameters were obtained from all patients; however, all women had at least two Doppler parameters evaluated. A limitation of this study is that the sample size did not provide sufficient power to detect differences in the prediction performance of different Doppler parameters. For example, the detec-

tion of early SGA fetuses among those with an EFW <10th percentile, demonstrating a significant improvement in sensitivity from 0.29 for UtA-PI to 0.69 for CPR (at the same FPR of about 10%), would have required 28 cases to provide a power of 80%, while only 18 cases were available in this study's cohort. As in all observational studies, causation cannot be determined apart from association.

Conclusion

At 20–24 weeks of gestation, an abnormal CPR (<5th percentile) identifies one-half of the fetuses destined to be diagnosed as SGA <34 weeks at 7% FPR (a 15.4-fold increase in the RR).

Acknowledgments

This research was supported, in part, by the Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS) and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HH-SN275201300006C. The ultrasound experience and technical support of senior registered diagnostic medical sonographers Catherine Ducharme and Denise Haggerty are gratefully acknowledged.

Disclosure Statement

The authors report no conflicts of interest.

References

- 1 Lumey LH: Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. *Paediatr Perinat Epidemiol* 1992;6:240–253.
- 2 Stein AD, Ravelli AC, Lumey LH: Famine, third-trimester pregnancy weight gain, and intrauterine growth: the Dutch Famine Birth Cohort Study. *Hum Biol* 1995;67:135–150.
- 3 Lang U, Baker RS, Khoury J, Clark KE: Effects of chronic reduction in uterine blood flow on fetal and placental growth in the sheep. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R53–R59.
- 4 Williams SJ, Hemmings DG, Mitchell JM, McMillen IC, Davidge ST: Effects of maternal hypoxia or nutrient restriction during pregnancy on endothelial function in adult male rat offspring. *J Physiol* 2005;565:125–135.
- 5 Peeters LL, Sheldon RE, Jones MD Jr, Makowski EL, Meschia G: Blood flow to fetal organs as a function of arterial oxygen content. *Am J Obstet Gynecol* 1979;135:637–646.
- 6 Reuss ML, Rudolph AM: Distribution and recirculation of umbilical and systemic venous blood flow in fetal lambs during hypoxia. *J Dev Physiol* 1980;2:71–84.
- 7 Sidi D, Kuipers JR, Teitel D, Heymann MA, Rudolph AM: Developmental changes in oxygenation and circulatory responses to hypoxemia in lambs. *Am J Physiol* 1983;245:H674–H682.
- 8 Wladimiroff JW, vd Wijngaard JA, Degani S, Noordam MJ, van Eyck J, Tonge HM: Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. *Obstet Gynecol* 1987;69:705–709.
- 9 Di Renzo GC, Luzi G, Cucchia GC, Caserta G, Fusaro P, Perdikaris A, Cosmi EV: The role of Doppler technology in the evaluation of fetal hypoxia. *Early Hum Dev* 1992;29:259–267.
- 10 Lang U, Baker RS, Khoury J, Clark KE: Fetal umbilical vascular response to chronic reductions in uteroplacental blood flow in late-term sheep. *Am J Obstet Gynecol* 2002;187:178–186.

- 11 Link G, Clark KE, Lang U: Umbilical blood flow during pregnancy: evidence for decreasing placental perfusion. *Am J Obstet Gynecol* 2007;196:489.e1–e7.
- 12 Cheema R, Dubiel M, Gudmundsson S: Fetal brain sparing is strongly related to the degree of increased placental vascular impedance. *J Perinat Med* 2006;34:318–322.
- 13 Akalin-Sel T, Nicolaides KH, Peacock J, Campbell S: Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. *Obstet Gynecol* 1994;84:439–444.
- 14 Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E: Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011;117:618–626.
- 15 Eixarch E, Meler E, Iraola A, Illa M, Crispi F, Hernandez-Andrade E, Gratacos E, Figueras F: Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. *Ultrasound Obstet Gynecol* 2008;32:894–899.
- 16 Cruz-Martinez R, Figueras F, Benavides-Serralde A, Crispi F, Hernandez-Andrade E, Gratacos E: Sequence of changes in myocardial performance index in relation to aortic isthmus and ductus venosus Doppler in fetuses with early-onset intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2011;38:179–184.
- 17 Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E: Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. *Ultrasound Obstet Gynecol* 2011;37:191–195.
- 18 Cruz-Lemini M, Crispi F, Van Mieghem T, Pedraza D, Cruz-Martinez R, Acosta-Rojas R, Figueras F, Parra-Cordero M, Deprest J, Gratacos E: Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. *Fetal Diagn Ther* 2012;32:116–122.
- 19 Demicheva E, Crispi F: Long-term follow-up of intrauterine growth restriction: cardiovascular disorders. *Fetal Diagn Ther* 2014;36:143–153.
- 20 Karsdorp VH, van Vugt JM, van Geijn HP, Kostense PJ, Arduini D, Montenegro N, Todoros T: Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet* 1994;344:1664–1668.
- 21 Alfrevic Z, Stampalija T, Gyte GM: Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2010;1:CD007529.
- 22 Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS: Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. *Ultrasound Obstet Gynecol* 2011;37:135–142.
- 23 Odibo AO, Goetzinger KR, Cahill AG, Odibo L, Macones GA: Combined sonographic testing index and prediction of adverse outcome in preterm fetal growth restriction. *Am J Perinatol* 2014;31:139–144.
- 24 Society for Maternal-Fetal Medicine Publications Committee, Berkley E, Chauhan SP, Abuhamad A: Doppler assessment of the fetus with intrauterine growth restriction. *Am J Obstet Gynecol* 2012;206:300–308.
- 25 Alfrevic Z, Stampalija T, Gyte GM: Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev* 2010;8:CD001450.
- 26 American College of Obstetricians and Gynecologists: ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol* 2013;121:1122–1133.
- 27 De Paco C, Ventura W, Oliva R, Miguel M, Arteaga A, Nieto A, Delgado JL: Umbilical artery Doppler at 19 to 22 weeks of gestation in the prediction of adverse pregnancy outcomes. *Prenat Diagn* 2014;34:711–715.
- 28 Hadlock FP, Deter RL, Harrist RB, Park SK: Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984;152:497–501.
- 29 Chauhan SP, Magann EF: Screening for fetal growth restriction. *Clin Obstet Gynecol* 2006;49:284–294.
- 30 Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B: ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol* 2013;41:233–239.
- 31 Gotsch F, Cruciani L, Ghezzi F, Ogge G, Yeo L, Romero R: Doppler interrogation of the fetal circulation; in Fleischer AC, Toy EC, Lee W, Manning FA, Romero R (eds): *Sonography in Obstetrics and Gynecology*, ed 7. New York, McGraw Hill, 2011, pp 257–308.
- 32 Savchev S, Figueras F, Sanz-Cortes M, Cruz-Lemini M, Triunfo S, Botet F, Gratacos E: Evaluation of an optimal gestational age cut-off for the definition of early- and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014;36:99–105.
- 33 Figueras F, Gratacos E: Stage-based approach to the management of fetal growth restriction. *Prenat Diagn* 2014;34:655–659.
- 34 Crovetto F, Triunfo S, Crispi F, Rodriguez-Sureda V, Roma E, Dominguez C, Gratacos E, Figueras F: First-trimester screening with specific algorithms for early- and late-onset fetal growth restriction. *Ultrasound Obstet Gynecol* 2016;48:340–348.
- 35 Alexander GR, Kogan MD, Himes JH: 1994–1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. *Matern Child Health J* 1999;3:225–231.
- 36 Stampalija T, Gyte GM, Alfrevic Z: Utero-placental Doppler ultrasound for improving pregnancy outcome. *Cochrane Database Syst Rev* 2010;9:CD008363.
- 37 Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH: One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000;96:559–564.
- 38 Gomez O, Figueras F, Martinez JM, del Rio M, Palacio M, Eixarch E, Puerto B, Coll O, Cararach V, Vanrell JA: Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. *Ultrasound Obstet Gynecol* 2006;28:802–808.
- 39 Poon LC, Lesmes C, Gallo DM, Akolekar R, Nicolaides KH: Prediction of small-for-gestational-age neonates: screening by biophysical and biochemical markers at 19–24 weeks. *Ultrasound Obstet Gynecol* 2015;46:437–445.
- 40 Triunfo S, Crovetto F, Rodriguez-Sureda V, Scazzocchio E, Crispi F, Dominguez C, Gratacos E, Figueras F: Changes in uterine artery Doppler velocimetry and circulating angiogenic factors in the first half of pregnancies delivering a small-for-gestational-age neonate. *Ultrasound Obstet Gynecol* 2017;49:357–363.
- 41 Pardi G, Cetin I, Marconi AM, Lanfranchi A, Bozzetti P, Ferrazzi E, Buscaglia M, Battaglia FC: Diagnostic value of blood sampling in fetuses with growth retardation. *N Engl J Med* 1993;328:692–696.
- 42 Donner C, Vermeylen D, Kirkpatrick C, de Maertelaer V, Rodesch F: Management of the growth-restricted fetus: the role of noninvasive tests and fetal blood sampling. *Obstet Gynecol* 1995;85:965–970.
- 43 Marsal K: Intrauterine growth restriction. *Curr Opin Obstet Gynecol* 2002;14:127–135.
- 44 Williams KP, Farquharson DF, Bebbington M, Dansereau J, Galerneau F, Wilson RD, Shaw D, Kent N: Screening for fetal well-being in a high-risk pregnant population comparing the nonstress test with umbilical artery Doppler velocimetry: a randomized controlled clinical trial. *Am J Obstet Gynecol* 2003;188:1366–1371.
- 45 Marsal K: Obstetric management of intrauterine growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2009;23:857–870.
- 46 Story L, Sankaran S, Mullins E, Tan S, Russell G, Kumar S, Kyle P: Survival of pregnancies with small for gestational age detected before 24 weeks gestation. *Eur J Obstet Gynecol Reprod Biol* 2015;188:100–103.

- 47 Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, Nicolaides KH, Harman CR, Baschat AA: Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008;32:160–167.
- 48 Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD: Predictable progressive Doppler deterioration in IUGR: does it really exist? *Am J Obstet Gynecol* 2013;209:539.e1–e7.
- 49 Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD: Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. *Am J Obstet Gynecol* 2013;208:290.e1–e6.
- 50 Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G: The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999;180:750–756.
- 51 Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GA: Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. *J Ultrasound Med* 2005;24:1223–1228.
- 52 DeVore GR: The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. *Am J Obstet Gynecol* 2015;213:5–15.
- 53 Figueras F, Gratacos E: Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014;36:86–98.
- 54 Morales-Rosello J, Khalil A, Morlando M, Papageorgiou A, Bhide A, Thilaganathan B: Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. *Ultrasound Obstet Gynecol* 2014;43:303–310.
- 55 Prior T, Paramasivam G, Bennett P, Kumar S: Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? *Ultrasound Obstet Gynecol* 2015;46:460–464.
- 56 Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorgiou A, Bhide A, Thilaganathan B: The association between fetal Doppler and admission to neonatal unit at term. *Am J Obstet Gynecol* 2015;213:57.e1–e7.
- 57 Khalil A, Morales-Rosello J, Townsend R, Morlando M, Papageorgiou A, Bhide A, Thilaganathan B: Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss. *Ultrasound Obstet Gynecol* 2016;47:74–80.
- 58 Triunfo S, Crispi F, Gratacos E, Figueras F: Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcome by fetoplacental Doppler at 37 weeks' gestation. *Ultrasound Obstet Gynecol* 2017;49:364–371.
- 59 Khalil A, Thilaganathan B: Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. *Best Pract Res Clin Obstet Gynaecol* 2017;38:38–47.
- 60 Flatley C, Greer RM, Kumar S: The magnitude of change in the fetal cerebroplacental ratio in the third trimester and the risk of adverse pregnancy outcome. *Ultrasound Obstet Gynecol* 2016, Epub ahead of print.
- 61 Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH: Umbilical and fetal middle cerebral artery Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2015;45:409–420.
- 62 Morales-Rosello J, Khalil A, Morlando M, Bhide A, Papageorgiou A, Thilaganathan B: Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2015;45:156–161.
- 63 Warshak CR, Masters H, Regan J, DeFranco E: Doppler for growth restriction: the association between the cerebroplacental ratio and a reduced interval to delivery. *J Perinatol* 2015;35:332–337.
- 64 Ropacka-Lesiak M, Korbela T, Swider-Musielak J, Breborowicz G: Cerebroplacental ratio in prediction of adverse perinatal outcome and fetal heart rate disturbances in uncomplicated pregnancy at 40 weeks and beyond. *Arch Med Sci* 2015;11:142–148.
- 65 Akolekar R, Syngelaki A, Gallo DM, Poon LC, Nicolaides KH: Umbilical and fetal middle cerebral artery Doppler at 35–37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2015;46:82–92.
- 66 Spinillo A, Gardella B, Bariselli S, Alfei A, Sili ni EM, Bello BD: Cerebroplacental Doppler ratio and placental histopathological features in pregnancies complicated by fetal growth restriction. *J Perinat Med* 2014;42:321–328.
- 67 Flood K, Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD: The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study. *Am J Obstet Gynecol* 2014;211:288.e1–288.e5.
- 68 Monteith C, Flood K, Mullers S, Unterscheider J, Breathnach F, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD: Evaluation of normalization of cerebroplacental ratio as a potential predictor for adverse outcome in SGA fetuses. *Am J Obstet Gynecol* 2017;216:285.e1–285.e6.
- 69 Espinoza J, Romero R, Nien JK, Gomez R, Kusanovic JP, Goncalves LF, Medina L, Edwin S, Hassan S, Carstens M, Gonzalez R: Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor. *Am J Obstet Gynecol* 2007;196:326.e1–e13.
- 70 Romero R, Deter R: Should serial fetal biometry be used in all pregnancies? *Lancet* 2015;386:2038–2040.