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ORIGINAL ARTICLE

The influence of fetal sex on the antenatal diagnosis of small for gestational age

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ABSTRACT

Objective: We evaluated the influence of fetal sex on the antenatal diagnosis and detection of small for gestational age (SGA).

Methods: The cohort consisted of unselected singleton pregnancies, undergoing routine biometry and cerebroplacental ratio (CPR) assessment at 36 weeks. Locally fitted equations for centiles and *Z* scores were used. "Ultrasound SGA" was defined as estimated fetal weight (EFW) < 10th centile, "SGA at birth" as birthweight (BW) < 10th centile adjusted for sex.

Results: Among 4112 pregnancies, there were 235 female "ultrasound SGA" fetuses and 177 male; (odds ratios (OR) 1.502 (1.223 – 1.845)); the detection rate of SGA at birth was 50.6% and 40.9%, respectively (OR 1.479 (0.980 – 2.228)). In "ultrasound SGA" girls the abdominal circumference growth velocity (ACGV) between 20 and 36 weeks was less frequently in the lowest decile (OR 0.490 (0.320 – 0.750)), with no differences in CPR.

Conclusions: Females are more commonly diagnosed as SGA; those diagnosed may be at less risk than males.

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KEYWORDS
Abdominal circumference; fetal sex; growth velocity; small for gestational age

Introduction

Placental dysfunction accounts for more than 50% of stillbirths [1]. In many, but not all cases, this is manifested as small for gestational age (SGA) [1,2] usually defined as estimated fetal weight (EFW) below the 10th centile [3] using a predefined growth standard. The identification of these babies *in utero* is still relatively poor in many countries; in the UK, for instance, it is the subject of quality improvement initiatives such as "Saving Babies Lives" [4]. Fetal growth assessment by universal third trimester ultrasound improves the antenatal detection of SGA [5]. Although an improvement in perinatal outcomes has not yet been demonstrated [3,6,7], and indeed the potential exists for increased intervention [8], the use of third trimester ultrasound is likely to increase in an attempt to identify SGA babies.

The *in utero* growth of male babies is greater [9] and their mean birthweight at term is higher by around 100 g compared to females [10]. Yet it is known that males are more at risk of multiple adverse pregnancy outcomes [11–13]. "Customization" of estimated fetal weight according to other physiological determinants of fetal weight has been proposed, yet this does not usually take account of fetal sex. This is in stark contrast to postnatal weight standards, which are always adjusted by sex. Using a common SGA threshold in prenatal ultrasound would intuitively suggest that a larger percentage of female fetuses are likely to fall below the 10th centile compared with boys.

The objective of this study was to compare male and female fetuses from an unselected population of women undergoing universal third trimester ultrasound with regards to (1) the incidence and accuracy of an antenatal diagnosis of SGA; and (2) the distribution of other potential markers of placental dysfunction such as growth velocity [5] and cerebroplacental ratio [14] in SGA fetuses.

Materials and methods

This is an observational study of an unselected cohort of women receiving pregnancy care and fetal ultrasound in a large, tertiary hospital in UK. All women are offered a first trimester dating scan, a detailed 20-week anomaly scan and a universal 36 weeks scan. Other ultrasound examinations are performed

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according to perceived clinical need. Ultrasound examinations are carried out by accredited sonographers or clinical fellows competent in fetal biometry and Doppler sonography. Measurements are recorded prospectively using commercially available archiving software (Viewpoint, GE Healthcare, Chicago, IL). Ultrasound reports are available to the clinicians as part of routine pregnancy care. This study was granted Institutional Review Board approval reference 4436 on 2 May 2017; patient consent was not required.

Maternal demographic characteristics are recorded at the booking prenatal visit. Pregnancies are dated by crown-rump length (CRL) estimation prior to 14 weeks or by head circumference after 14 weeks. Standard fetal biometry including biparietal diameter, head circumference, abdominal circumference (AC), and femur length is performed at 20 and 36 weeks gestation. Ultrasonographic plane definitions, measurement methodology and image quality control follow the recommendations of the INTERGROWTH 21st study [15].

The 20-week gestational window is 19 + 0to 21 + 6 weeks; the 36 weeks window is 35 + 0 to 36 + 6 weeks. The four-parameter Hadlock equation is used for EFW estimation [16]. Universal Doppler investigations at the 36 weeks scan include the pulsatility index (PI) of a free loop of the umbilical artery (UA) during fetal quiescence; and the PI of the proximal middle cerebral artery (MCA) [17]. The cerebroplacental ratio (CPR) is defined as the ratio between MCA and UA PI [14]. Birthweight (BW) and sex are recorded at birth.

For this study, only singleton pregnancies with complete paired biometry who delivered at over 35 + 0-week gestation were used. Fetal anomaly and aneuploidy screening programes are in place in our institution. Included pregnancies were determined antenatally not to have chromosomal or major structural abnormalities. No further exclusions were made.

The AC, EFW, and BW data were extracted and modelled separately at each gestational window, in order to produce locally fitted equations of the mean and SD using the Altman–Royston method [18]. Linear, quadratic, and cubic equations were tested with gestational age in exact days (GA) as the independent variable. Goodness of fit was confirmed by assessment of the regression coefficients (R^2), by visual inspection of regression curves for biological plausibility and by demonstrating that around 9–10% of measurements fall below the fitted 10th centile for each variable. AC and EFW data were modelled independently of sex, whereas BW was modelled separately for boys and girls. "Ultrasound SGA" was defined as EFW below the 10th centile at 36 weeks; "SGA at birth" was defined as BW below the sex-adjusted 10th centile.

AC measurements were transformed into *Z*-scores using the locally derived mean and SD and the formula Z score = (observed AC − fitted mean)/SD. AC growth velocity (ACGV) between 20 and 36 weeks was defined as the *Z*-score difference divided by the interval in days and multiplied by 100. The lowest decile for ACGV of −1.3091 [19] was used to identify fetuses with a clinically significant AC deceleration. Centile ranges for UA PI, MCA PI, and CPR were used from published references [20,21].

Distribution of continuous variables was checked for normality by histogram inspection. Continuous variables were compared between boys and girls using the Student *t*-test. Frequencies of categorical variables were compared using the two-sided Fisher's exact test and odds ratios (OR) with their 95% confidence intervals were reported. A standard level of statistical significance $p < .05$ was used. Data were analyzed and figures were produced using IBM SPSS version 23 (SPSS Inc, Chicago, IL).

Results

A total of 4112 singleton pregnancies underwent complete paired biometry and subsequently delivered at over 35 + 0-week gestation, between September 2016 and June 2017. Table 1 summarizes relevant maternal characteristics. Fetal characteristics are summarized in Table 2. Due to the narrow gestational windows, a simple linear regression model provided the best fit for the mean and SD of AC, EFW, and BW on every occasion. Following modelling, the number of cases with AC, EFW, and BW below the locally fitted 10th centile was calculated and confirmed goodness of fit (Table 2).

Among 412 cases of ultrasound SGA, there were 235 female against 177 male fetuses; $p < .001$, OR 1.502 (1.223–1.845) (Table 3). The distribution of EFW expressed as Z scores for boys and girls is shown in Figure 1. Using the 10th centile as a common EFW threshold identified 11.9% of the total female cohort as SGA, but identified only 8.3% of the male cohort.

Table 1. Basic maternal characteristics.

	Mean ± SD or *N* (%)	Valid (*N*)	Missing (*N*)
Age (y)	31.3 ± 5.3	4112	0
Height (cm)	165.3 ± 7.9	4085	27
Weight at booking (kg)	70.1 ± 18.8	4085	27
BMI at booking (kg/m^2)	26.6 ± 8.3	4082	30
Smoking	368 (9%)	4085	27
Parity			
Nulliparous	1797 (43.7%)	4112	0
Multiparous	2315 (56.3%)		

(BMI: body mass index; SD: standard deviation; ART: assisted reproductive technology; IVF: *in vitro* fertilization.

Conversely there were 372 babies who were SGA at birth (defined as BW <10th centile adjusted by sex). The overall detection rate of SGA at birth was 45.4% (Table 3). The detection rate of SGA at birth for boys and girls was 40.9% and 50.6% ($p = .076$); the true positive rate of ultrasound SGA was 45.8% and 37.4%, respectively ($p = .105$).

Among 412 ultrasound SGA cases, the mean ACGV was −0.90 (range −4.07 to 1.26). However, there was a significant difference with boys demonstrating larger growth deceleration compared with girls, mean ACGV of −1.15 versus −0.72, respectively; $p < .001$. Girls were less likely to have ACGV in the lowest decile $p = .001$, OR 0.490 (0.320–0.750). There were no significant differences of mean UA PI ($p = .950$), MCA PI ($p = .773$) or CPR ($p = .656$) between male and female fetuses. Table 4 summarizes the categorical parameters thought to be markers of placental dysfunction for male and female SGA fetuses.

Table 2. Basic fetal characteristics.

	Mean (range) or *N* (%)	Valid *N*	Missing *N* (%)
GA −20 week scan	20.3 (19.0–21.9)	4112	0 (0%)
GA −36 week scan	36.1 (35.1–36.7)	4112	0 (0%)
GA at delivery	40.0 (35.3–43.1)	4112	0 (0%)
Birthweight	3503 (1675–5375)	4112	0 (0%)
AC <10th centile −20 weeks	410 (10%)	4112	0 (0%)
AC <10th centile −36 weeks	375 (9.1%)	4112	0 (0%)
EFW <10th centile −36 weeks	412 (10%)	4112	0 (0%)
EFW <3rd centile −36 weeks	107 (2.6%)	4112	0 (0%)
UA PI >95th centile −36 weeks	117 (2.8%)	4112	0 (0%)
MCA PI <5th centile −36 weeks	214 (5.2%)	3987	125 (3%)
CPR <5th centile −36 weeks	81 (2%)	3987	125 (3%)
Birthweight <10th centile	372 (9.0%)	4112	0 (0%)
Male sex	2141 (52.1%)	4112	0 (0%)
Female sex	1971 (47.9%)	4112	0 (0%)

GA: gestational age; AC: abdominal circumference; EFW: estimated fetal weight; UA PI: umbilical artery; MCA: middle cerebral artery; PI: pulsatility index; CPR: cerebroplacental ratio.

Discussion

This study has demonstrated that the use of a universal EFW threshold for both sexes leads to a significant

Table 3. (A) Antenatal diagnosis of SGA (EFW <10th centile), (B) Detection rate of SGA (EFW <10th centile) using as gold standard SGA at birth, (C)True positive rate of SGA (EFW <10th centile) using as gold standard SGA at birth (BW <10th centile).

	Overall	Male	Female	Odds ratio (95%CI)	*p*
(A)					
Total babies	4112	2141	1971		
Screen positive SGA	412	177 (42.9%)	235 (57.1%)	1.502 (1.223–1.845)	.001
Screen negative SGA	3700	1964 (53.1%)	1736 (46.9%)		
(B)					
Total SGA at birth	372	198	174		
Screen positive SGA	169	81 (40.9%)	88 (50.6%)	1.479 (0.980–2.228)	
Screen negative SGA	203	117 (59.1%)	86 (49.4%)		.076
(C)					
Screen positive SGA	412	177	235		
BW <10th	169	81 (45.8%)	88 (37.4%)	1.409 (0.948–2.095)	.105
BW >10th	243	96 (54.2%)	147 (62.6%)		

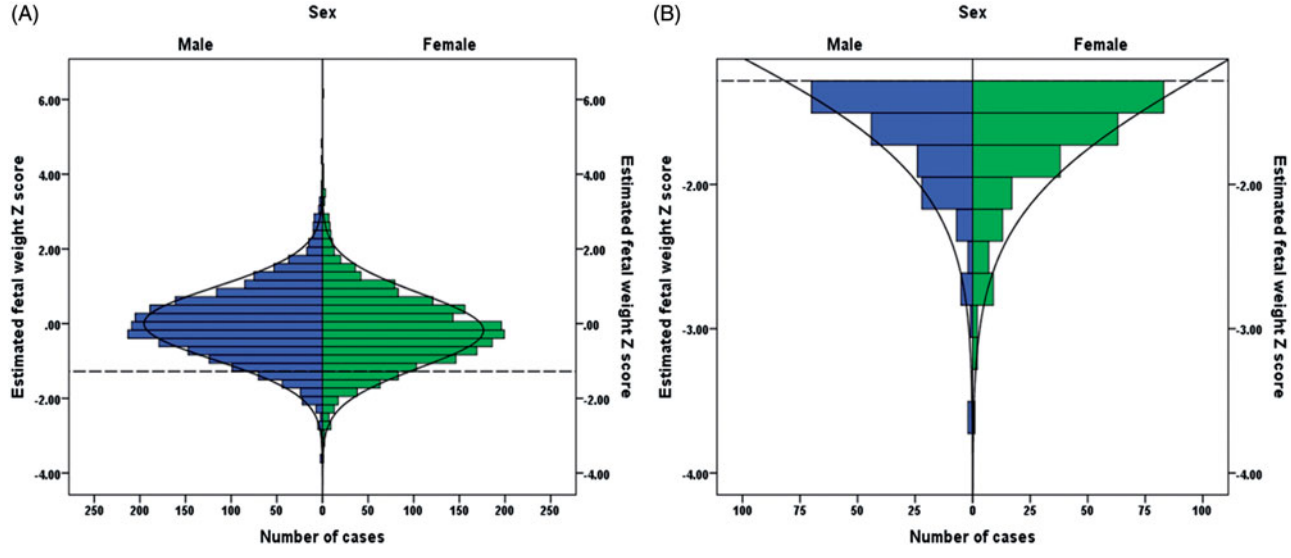

Figure 1. (A) Distribution of estimated fetal weight *Z* score at 36 weeks by sex for the entire cohort and (B) for fetuses below the 10th centile; the dotted line indicates *Z* score =1.282 which is the 10th centile.

Table 4. Potential markers of placental dysfunction among male and female screen positive SGA fetuses.

	Male	Female	Odds ratio (95%CI)	*p*
Lowest decile ACGV	69 (39.0%)	56 (23.8%)	0.490 (0.320–0.750)	.001
EFW <3rd centile	46 (26.0%)	61 (26.0%)	0.998 (0.640–1.558)	1.000
UA PI >95th centile	13 (7.3%)	18 (7.7%)	1.046 (0.498–2.197)	1.000
MCA PI <5th centile	15 (8.7%)	18 (7.8%)	0.889 (0.434–1.818)	.855
CPR <5th centile	11 (6.4%)	15 (6.5%)	1.021 (0.457–2.283)	1.000

SGA: small for gestational age; AC: abdominal circumference; EFW: estimated fetal weight; UA: umbilical artery; MCA: middle cerebral artery; PI: pulsatility index; CPR: cerebroplacental ratio.

over-representation of female fetuses as SGA and therefore potentially to obstetric intervention. This also has the potential to adversely affect overall SGA detection rates. Further, the differences in ACGV, a marker of adverse outcome [5], although not in CPR, suggest that females identified as SGA may not be at the same level of perinatal risk as SGA boys.

Small fetuses are at an increased risk of term antepartum stillbirth [1]. Accurate identification followed by early delivery should result in reduction of perinatal mortality. Indeed, common and recommended obstetric practice is to deliver these babies at 37–38 weeks [3]. Routine universal ultrasound is superior to selective ultrasound for the diagnosis of SGA, yet consecutive systematic reviews have failed to demonstrate a benefit in perinatal mortality [6]. There may be several reasons for this, including inaccuracies in ultrasound and uncertainty about timing. Perhaps most importantly, a statistical definition of SGA (i.e. a percentile threshold) will not only include some fetuses at risk of adverse perinatal outcome due to placental dysfunction, but also a significant proportion of fetuses who are constitutionally small and healthy. In these latter fetuses, obstetric intervention might inadvertently increase neonatal morbidity [8]. Our data suggest that these are more likely to be girls and that this phenomenon could be contributing to the perceived failure of ultrasound biometry in reducing perinatal risk.

Further, it has been a consistent biological finding that males have higher rates of adverse outcomes [11–13]. Simchen et al. [13] demonstrated that term males were associated with increased risk of postnatal neurological complications, especially where SGA. Cerebral palsy and neonatal mortality rates are higher in males [22]. Yet using a sex-unadjusted EFW threshold leads to under-representation of males.

Universally accepted birthweight standards have long demonstrated that male babies are on average heavier than female ones. "Customization" for fetal sex is a not a new concept [23]. Monier et al. [24] analyzing data from the French National Perinatal Survey, found that female babies were more likely to be suspected of FGR than males. Rizzo et al. [25] constructed sex-specific antenatal charts, which were also customized according to GROW [26] principles, and postulated their usage would improve SGA detection. However, most widely accepted sonographic models for SGA detection do not consider fetal sex in the equation [16,27,28]. Adjustment for fetal sex is not part of the current GROW program while other determinants of fetal growth are; some of those determinants, such as ethnicity, are more controversial. The importance of fetal sex is perhaps lost in the debate. The result, as we demonstrate, is that female fetuses are over-represented as SGA. The reduced incidence of low ACGV suggests that ultrasound SGA females are more likely to be constitutionally small and therefore may be at less perinatal risk; conversely "at risk" male babies are more likely to go undetected.

Our study has strengths. This is an unselected cohort of women receiving universal third trimester ultrasound and therefore is free of bias. All ultrasound data are prospectively collected. Quality control measures such as image reviewing and remeasurement are established in our institution. Locally fitted equations for the 10th centile and *Z* scores were produced instead of using published references. This was to avoid the phenomenon where a baby can have different centile position before or after birth due to methodological differences between different published charts.

We also acknowledge limitations. With any observational study there is potential for unaccounted bias and confounding. We used ACGV and CPR as surrogate markers of placental dysfunction, instead of using perinatal outcomes of morbidity or indeed mortality. Postnatal outcomes would be influenced not only by the adverse impact of "maleness" but also by the confounding effect of obstetric interventions around the time of delivery. Our aim here was to assess how fetal sex influences screening at the point of diagnosis. SGA fetuses with abnormal CPR have a higher rate of adverse outcomes [29–31]. Indeed, this marker has been shown to identify babies that are not necessarily SGA but are nevertheless at increased risk [32,33]. The ACGV is also recognized as an important determinant of adverse perinatal outcome in SGA fetuses [5,34]. ACGV and CPR are therefore established pathophysiological markers of placental dysfunction in late third trimester and, although not widely used in routine care, they are useful determinants of the fetus at risk.

A potential problem with prenatal sex adjustment is that parents may not want to know the fetal sex before birth; more serious would be parental bias in favor of one sex. These could be at least partly overcome by allocation of sex-adjusted centile or indeed

alteration of management, without antenatal revelation of fetal sex. The potential problems with adjustment for sex should be compared to the potential benefits.

Ultrasound in the third trimester is the key to the identification of the SGA fetus. Simply identifying and delivering small babies will have limited impact on mortality and morbidity, as well as adverse consequences through increased intervention. Modeling, using newer discriminators of risk, such as the CPR, ACGV, or biomarkers, may improve the sensitivity and specificity of antenatal assessment of placental dysfunction beyond that achieved by EFW alone. This modeling is likely to perform better if it includes fetal sex, because of its effect on both the fetal weight and its independent effect on outcomes.

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Disclosure statement

The authors report no conflict of interest.

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