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Characteristics associated with antenatally unidentified small-for-gestational-age fetuses: prospective cohort study nested within DESiGN randomized controlled trial

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KEYWORDS: antenatal screening; estimated fetal weight; fetal growth; maternal characteristics; risk factors; SGA; small-for-gestational age; ultrasound patterns

CONTRIBUTION

What are the novel findings of this work?
Pregnancies with unidentified small-for-gestational-age (SGA) fetuses were less likely to have an indication for serial scan and more likely to have a body mass index of 25.0–29.9 kg/m^2, less severe SGA and cephalic presentation at birth. Two-thirds of SGA pregnancies had no serial scan indication, which emphasizes the importance of an accurate screening strategy for low-risk women.

What are the clinical implications of this work?
Unidentified SGA is more likely in overweight women and those without a serial scan indication. Missed-case analysis is important to investigate unidentified SGA amongst women with risk factors but no serial scans. Further research should determine how to improve SGA detection for women who are overweight or low risk.

ABSTRACT

Objective *To identify the clinical characteristics and patterns of ultrasound use amongst pregnancies with an antenatally unidentified small-for-gestational-age (SGA) fetus, compared with those in which SGA is identified, to understand how to design interventions that improve antenatal SGA identification.*

Methods *This was a prospective cohort study of singleton, non-anomalous SGA (birth weight < 10th centile) neonates born after 24 + 0 gestational weeks at 13 UK sites, recruited for the baseline period and control arm of the DESiGN trial. Pregnancy with antenatally unidentified SGA was defined if there was no scan or if the final scan showed estimated fetal weight (EFW) at the 10th centile or above. Identified SGA was defined if EFW was below the 10th centile at the last scan. Maternal and fetal sociodemographic and clinical characteristics were studied for associations with unidentified SGA using unadjusted and adjusted logistic regression models. Ultrasound parameters (gestational age at first growth scan, number and frequency of ultrasound scans) were described, stratified by presence of indication for serial ultrasound. Associations of unidentified SGA with absolute centile and percentage weight difference between the last scan and birth were also*

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studied on unadjusted and adjusted logistic regression, according to time between the last scan and birth.

Results *Of the 15 784 SGA babies included, SGA was not identified antenatally in 78.7% of cases. Of pregnancies with unidentified SGA, 47.1% had no recorded growth scan. Amongst 9410 pregnancies with complete data on key maternal comorbidities and antenatal complications, the risk of unidentified SGA was lower for women with any indication for serial scans (adjusted odds ratio (aOR), 0.56 (95% CI, 0.49–0.64)), for Asian compared with white women (aOR, 0.80 (95% CI, 0.69–0.93)) and for those with non-cephalic presentation at birth (aOR, 0.58 (95% CI, 0.46–0.73)). The risk of unidentified SGA was highest among women with a body mass index (BMI) of 25.0–29.9 kg/m^2 (aOR, 1.15 (95% CI, 1.01–1.32)) and lowest in those with underweight BMI (aOR, 0.61 (95% CI, 0.48–0.76)) compared to women with BMI of 18.5–24.9 kg/m^2. Compared to women with identified SGA, those with unidentified SGA had fetuses of higher SGA birth-weight centile (adjusted odds for unidentified SGA increased by 1.21 (95% CI, 1.18–1.23) per one-centile increase between the 0th and 10th centiles). Duration between the last scan and birth increased with advancing gestation in pregnancies with unidentified SGA. SGA babies born within a week of the last growth scan had a mean difference between EFW and birth-weight centiles of 19.5 (SD, 13.8) centiles for the unidentified-SGA group and 0.2 (SD, 3.3) centiles for the identified-SGA group (adjusted mean difference between groups, 19.0 (95% CI, 17.8–20.1) centiles).*

Conclusions *Unidentified SGA was more common amongst women without an indication for serial ultrasound, and in those with cephalic presentation at birth, BMI of 25.0–29.9 kg/m^2 and less severe SGA. Ultrasound EFW was overestimated in women with unidentified SGA. This demonstrates the importance of improving the accuracy of SGA screening strategies in low-risk populations and continuing performance of ultrasound scans for term pregnancies.* © *2022 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The reduction of stillbirth and perinatal death rates is an international priority[1]. Between 30% and 50% of stillborn babies are small-for-gestational age (SGA; birth weight < 10th centile for gestational age)[2–7], and being SGA increases the risk of stillbirth 4-fold[8]. It is therefore accepted that improvements in antenatal detection of SGA fetuses and subsequent perinatal care are needed to reduce the rate of stillbirth[9].

Current strategies to screen for SGA (or fetal growth restriction (FGR)) during pregnancy involve fundal height measurement and targeted ultrasound for women at low risk of SGA/FGR, and serial fetal ultrasound assessment for women with risk factors for SGA/FGR[10]. This strategy is associated with a < 50% SGA detection rate[11–18]. Alternatively, universal serial ultrasound screening detects a higher proportion of SGA in research settings, but without replication in routine care[12,13].

Improving the rate of antenatal detection of SGA without consequential increase in false-positive diagnoses requires an understanding of maternal and perinatal characteristics of pregnancies in which SGA is not currently identified antenatally. Previous studies have found that FGR was more likely to be detected amongst parous women (particularly those with a previous FGR baby), women with lower BMI, those who had assisted conception[19] and if a third-trimester fetal growth scan had been conducted[20]. FGR was less likely to be detected if the fetal growth scan was falsely reassuring (EFW or abdominal circumference (AC) > 10th centile) and in women cared for in low-risk midwifery-led settings[20]. However, clinical characteristics included in either study were limited.

This study aimed to identify the clinical characteristics and patterns of ultrasound use amongst pregnancies in which SGA is not identified antenatally, compared with those in which SGA is identified, to understand how we can design interventions to improve detection.

METHODS

Study design

This was a prospective cohort study conducted using data on pregnancies and births collected for the DESiGN trial. DESiGN was a UK randomized cluster controlled trial conducted between 5 November 2016 and 28 March 2019, which compared the clinical effectiveness of the Growth Assessment Protocol (GAP) in the antenatal detection of SGA with that of standard care, finding no difference in primary outcome between the strategies and a weak economic case for replacing standard care with GAP[21,22]. Detailed descriptions of the trial and data collection methods have been published previously[21,23,24].

For this analysis, we included only those pregnancies in which the neonate had SGA (defined as birth weight below the 10th centile for gestational age on population reference charts[25]) after 24 + 0 gestational weeks and was not exposed to the intervention. This included all pregnancies from control clusters and any pregnancies in intervention clusters that occurred prior to the implementation of GAP. Multiple pregnancies (i.e. twins) and those with antenatally diagnosed fetal abnormalities were excluded. Women and babies in whom SGA detection status could not be determined because ultrasound data were missing during an entire trial phase at a cluster site (occurred at two clusters) were also excluded. This study has been reported according to the recommendations of the STROBE statement for observational studies[26].

Defining antenatally identified and unidentified cases of SGA

Antenatally unidentified SGA was defined as pregnancy in which the neonate was diagnosed as SGA at birth

(birth weight $< 10^{th}$ centile on population birth-weight charts[25]), but for which there was no evidence that an antenatal ultrasound diagnosis had been made, i.e. the woman did not undergo growth scans or EFW at the last fetal growth scan (defined as any scan with fetal biometry conducted after 24 + 0 weeks' gestation) was above the 10^{th} centile for gestational age. Identified SGA was defined as pregnancy in which antenatal diagnosis of SGA had been made correctly, i.e. EFW at the last fetal growth ultrasound was below the 10^{th} centile for gestational age. This outcome was chosen because clinical guidelines on the management of pregnancies with suspected SGA currently commonly apply the EFW $< 10^{th}$ centile threshold and decisions regarding timing and mode of birth are driven largely by EFW at the last scan. EFW was assessed using Hadlock fetal growth charts[27].

Exposures

The maternal and fetal characteristics studied include maternal age, index of socioeconomic deprivation quintile, race (black, white, Asian, mixed, other), BMI (< 18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, $\geq 40.0\,kg/m^2$), parity (0, 1, 2, 3, ≥ 4), smoking status, maternal comorbidity (pre-existing hypertension and diabetes), antenatal complication (pre-eclampsia, gestational hypertension, gestational diabetes (GDM)), low pregnancy-associated plasma protein-A (PAPP-A) (< 0.300, 0.300–0.415, > 0.415 multiples of the median (MoM)), non-cephalic presentation at birth and birth-weight centile (continuous or $< 3^{rd}$ centile, 3^{rd} to 4.9^{th} centile, 5^{th} to 10^{th} centile). Categories were chosen according to those used in routine clinical practice, including existing risk-stratification models. A composite exposure category was also developed to include any reported risk factor for SGA, indicating need for serial fetal growth scans during pregnancy (maternal age ≥ 40 years, BMI $\geq 35\,kg/m^2$, smoker, any of the above maternal comorbidities or antenatal complications, PAPP-A ≤ 0.415 MoM). The maternal comorbidities and antenatal complications were included because each raises the risk of SGA and is therefore an indication for serial fetal growth scans in pregnancy, although the list is limited to indications for which data were accessible.

To assess the patterns of ultrasound use when screening for SGA, only fetal growth scans at which EFW was calculated (or could be calculated using recorded biometry) after 24 + 0 gestational weeks were studied. Scans were categorized into screening and surveillance scans based on when EFW was first identified to be below the 10^{th} centile: all scans before and including the first scan with EFW $< 10^{th}$ centile were categorized as screening scans, while all scans after the scan at which EFW was first below the 10^{th} centile were categorized as surveillance scans.

The following characteristics were considered to assess the patterns of ultrasound use: gestational age at the time of first fetal growth scan, frequency of serial screening scans (mean and categorical: 3-week, 4-week, $>$ 4-week intervals), time between the last (screening or surveillance) scan and birth and difference between EFW at the last scan and birth weight, expressed in terms of absolute centiles (EFW centile – birth-weight centile) and as weight difference presented as a percentage of birth weight ((EFW – birth weight)/birth weight). The calculation of mean screening frequency accounted for different gestational ages at the time of commencing serial screening scans (e.g. because of indications that arise later in pregnancy), antenatal diagnosis of SGA that stops the screening period and birth itself by dividing the period from the first scan until the last screening scan by $n - 1$ (where n is the number of screening scans performed). For this analysis, only pregnancies that had at least two screening scans could be included.

Management of missing data

Patterns of missing data were summarized for each characteristic and outcome using descriptive statistics. Missing data were multiply imputed as described previously[24]. The primary analysis of factors associated with SGA detection status used imputed data on demographics and growth status, but comorbidities, antenatal complications and fetal presentation were not imputed and were therefore analyzed based on availability. If multiple imputation was used, only percentages and not numbers were provided (except to approximate the total number of included births for each analysis), since frequencies are averaged across 10 imputed datasets. Given that PAPP-A is an important characteristic (when low, it is an indication for serial fetal growth ultrasound), but there was wide variation in its availability, missing data on PAPP-A were included as an exposure category, and for analysis in which PAPP-A was studied, sites that did not provide data on it were excluded. For the study of ultrasound patterns, it was assumed that pregnancies without a record of a fetal growth scan did not undergo a scan (sensitivity analysis was conducted to test the impact of this assumption and is described below). Rubin's rules were used for analysis of imputed data[28].

Statistical analysis

The number and proportion of pregnancies in which the neonate was SGA at birth and in which this was diagnosed antenatally were calculated. Characteristics of pregnancies in which SGA was not identified were summarized using descriptive statistics (percentage or mean ± SD, as appropriate). Characteristics of pregnancies with unidentified SGA were then compared with those of pregnancies in which SGA was identified using unadjusted and adjusted logistic regression, with results presented as odds ratios. Adjustments were made using all other demographic and clinical characteristics (age, index of socioeconomic deprivation quintile, race, BMI, parity and smoking status), birth-weight centile of the neonate, and maternal comorbidities and antenatal complications. Given that the data were collected from a cluster trial population, all models were also adjusted for the cluster

site and trial phase to account for clustering and temporal changes.

Patterns of ultrasound use for screening were also summarized using descriptive statistics. However, for this analysis, adjustments were made using trial factors only (cluster site and trial phase). To determine the impact of ultrasound patterns on the rate of detection of SGA amongst women with and those without an indication for serial fetal ultrasound scans, the comparisons were stratified by the presence or absence of an indication; this available-case analysis was conducted amongst women who had complete information on presence or absence of comorbidities and antenatal complications, with antenatal care at sites that provided data on PAPP-A. Lastly, associations of unidentified SGA with absolute centile and percentage weight difference between the last scan and birth were studied on unadjusted and adjusted logistic regression, according to time between the last scan and birth.

Sensitivity analysis

The analyses were repeated to determine whether any of the methodological choices had influenced the findings. The analysis was first repeated using only observed (i.e. non-imputed) data (5307 women with complete data on comorbidities and antenatal complications, of which 4129 (77.8%) had unidentified SGA; larger sample ($n = 15\,247$) with complete data at least on SGA status for analysis of ultrasound patterns, with unidentified SGA in 11 897 (78.0%) cases). The second sensitivity analysis used only pregnancies ($n = 12\,122$, including 9164 (75.6%) with unidentified SGA) in which there was evidence of a presumed anomaly scan (scan conducted between $18 + 0$ and $24 + 0$ gestational weeks) to determine the effect of having continuous third-trimester care at the same cluster site and definite evidence of an ultrasound record. This second analysis was conducted to test the assumption that women who had no record of a fetal growth scan at the cluster site at which they gave birth had not undergone one at that site or elsewhere.

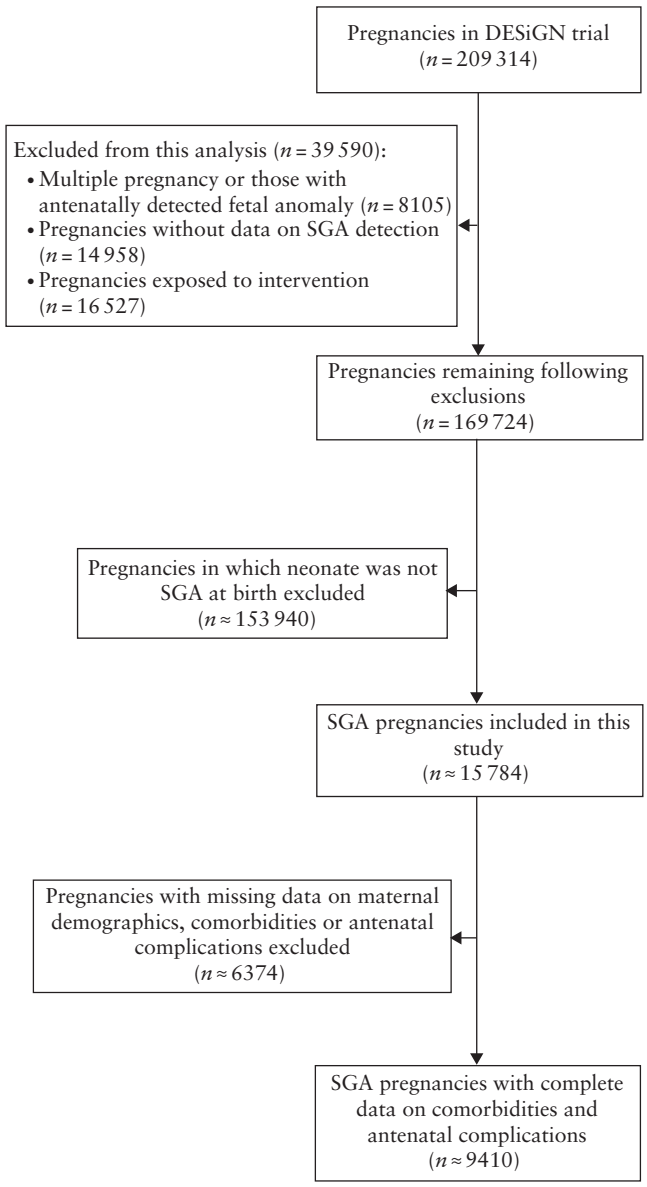

Figure 1 Flowchart summarizing study population of pregnancies (imputed data) in which neonate was diagnosed as small-for-gestational age (SGA) at birth, which were included from the DESiGN (DEtection of Small for GestatioNal age fetus) trial[21].

RESULTS

Of the 169 724 pregnancies included in the control arm of the DESiGN randomized controlled trial, 15 784 (9.3%) were SGA at birth and were included in this study. The characteristics, maternal and neonatal outcomes, and test performance statistics observed in the wider control arm of the trial population (including non-SGA births) during the baseline and outcome periods have been reported elsewhere[21]. Of these, SGA was not identified antenatally in ≈12 416 (78.7%) cases. Following exclusion of pregnancies with missing data on maternal comorbidities and antenatal complications, ≈9410 pregnancies were available for the assessment of maternal and fetal characteristics associated with unidentified SGA (Figure 1).

Factors associated with unidentified SGA

Maternal and perinatal characteristics are summarized in Table 1, according to SGA detection status. Amongst women in whom SGA was unidentified, there was a lower proportion of those aged 40 years or over (3.7% *vs* 5.2%), women with BMI < 18.5 kg/m^2 (5.0% *vs* 7.5%), smokers (8.7% *vs* 10.4%) or cases with any comorbidity (chronic hypertension, 1.9% *vs* 3.0%; pre-existing diabetes, 1.2% *vs* 2.1%; pre-eclampsia, 2.6% *vs* 6.9%; gestational hypertension, 1.8% *vs* 3.6%; GDM, 4.6% *vs* 6.8%). Overall, only 31.5% of women with a SGA neonate had any recorded indication for serial fetal growth ultrasound scans (68.5% had no known indication for serial scans); the rate was higher amongst women with identified SGA *vs* those with unidentified SGA (42.8% *vs* 28.5%; $P < 0.01$).

Table 1 Maternal and perinatal characteristics of pregnancies with complete data on maternal comorbidities and antenatal complications*, according to whether small-for-gestational age (SGA) was identified antenatally

Characteristic	*Unidentified SGA (n ≈ 7532)*	*Identified SGA (n ≈ 1878)*
Maternal age (years)	30.5 ± 5.5	30.9 ± 5.7
≤ 40 years	96.3	94.8
> 40 years	3.7	5.2
IMD quintile		
1 (least deprived)	9.0	10.8
2	11.7	12.7
3	24.8	23.6
4	35.6	33.4
5 (most deprived)	19.0	19.6
Race		
White	38.2	36.5
Black	16.9	17.0
Asian	31.8	33.8
Mixed	1.7	2.0
Other	11.4	10.6
BMI (kg/m^2)	25.0 ± 5.2	24.8 ± 5.6
< 18.5 kg/m^2	5.0	7.5
18.5–24.9 kg/m^2	52.9	52.2
25.0–29.9 kg/m^2	27.1	25.0
30.0–34.9 kg/m^2	10.0	9.9
35.0–39.9 kg/m^2	3.4	3.6
≥ 40.0 kg/m^2	1.6	1.9
Parity		
0	59.4	56.9
1	25.5	27.7
2	9.2	9.1
3	3.4	3.9
≥ 4	2.5	2.4
Smoker	8.7	10.4
Comorbidity		
Hypertension	1.9	3.0
Diabetes	1.2	2.1
Antenatal complication		
Pre-eclampsia	2.6	6.9
Gestational hypertension	1.8	3.6
Gestational diabetes	4.6	6.8
PAPP-A		
< 0.300 MoM	1.6	4.6
0.300–0.415 MoM	3.0	6.6
> 0.415 MoM	45.5	50.1
Missing data	49.8	38.7
Any indication for serial fetal scans	28.5	42.8
Cephalic presentation at birth	95.3	91.2
Gestational age at birth (weeks)	37.7 ± 3.0	39.8 ± 2.4
< 28 + 0 weeks	0.8	1.9
28 + 0 to 33 + 6 weeks	1.8	8.0
34 + 0 to 36 + 6 weeks	3.3	15.2
37 + 0 to 37 + 6 weeks	4.4	15.3
38 + 0 to 38 + 6 weeks	9.4	19.8
39 + 0 to 39 + 6 weeks	19.3	17.6
≥ 40 + 0 weeks	61.0	22.2
Birth-weight centile	5.4 ± 2.9	4.0 ± 2.8
< 3rd centile	24.9	43.5
3rd–4.9th centile	18.7	20.9
5th–10th centile	56.5	35.5

Data are given as % or mean ± SD. Data using multiply imputed datasets provide only percentages of characteristics of interest. Demographic characteristics of the trial population have been reported previously[21]. *Except for pregnancy-associated plasma protein-A (PAPP-A), for which data were missing in some cases. BMI, body mass index; IMD, index of socioeconomic deprivation; MoM, multiples of the median.

Unadjusted and adjusted comparisons of demographic characteristics and comorbidities or antenatal complications between pregnancies in which SGA was not identified antenatally *vs* those in which it was are presented in Tables 2 and 3. Following mutual adjustment for other factors, the risk of unidentified SGA was lower for women aged over 40 years (adjusted odds ratio (aOR), 0.74 (95% CI, 0.56–0.98); $P = 0.03$), women of Asian *vs* white race (aOR, 0.80 (95% CI, 0.69–0.93); global race, $P < 0.01$), smokers (aOR, 0.79 (95% CI, 0.66–0.96); $P = 0.02$), those with BMI < 18.5 kg/m^2 *vs* BMI of 18.5–24.9 kg/m^2 (aOR, 0.61 (95% CI, 0.48–0.76); global BMI, $P = 0.04$), those with pre-existing diabetes (aOR, 0.52 (95% CI, 0.34–0.79); $P < 0.01$), GDM (aOR, 0.64 (95% CI, 0.51–0.80); $P < 0.01$), gestational hypertension (aOR, 0.54 (95% CI, 0.39–0.74); $P < 0.01$), pre-eclampsia (aOR, 0.40 (95% CI, 0.31–0.51); $P < 0.01$), low PAPP-A (aOR, 0.45 (95% CI, 0.32–0.64) for < 0.300 MoM and aOR, 0.56 (95% CI, 0.43–0.75) for 0.300–0.415 MoM; $P < 0.01$ for both) or any indication for serial scans (composite aOR, 0.56 (95% CI, 0.49–0.64); $P < 0.01$). Compared to women with BMI of 18.5–24.9 kg/m^2, risk of missed SGA was significantly higher for women with BMI of 25.0–29.9 kg/m^2 (aOR, 1.15 (95% CI, 1.01–1.32)) and non-significantly higher for BMI of 30.0–34.9 kg/m^2 (aOR, 1.12 (95% CI, 0.91–1.38)) (global BMI, $P = 0.04$). An association was not observed for higher BMI categories, although these findings are limited by small numbers.

Overall, 9.7% of SGA neonates were born preterm (< 37 completed weeks' gestation). Compared with neonates in whom SGA was identified antenatally, neonates in whom SGA was not identified antenatally were less likely to be born at an early term, preterm and extremely preterm gestational age, and therefore were more likely to be born after 39 weeks' gestation. Of neonates in whom SGA was not identified antenatally, 61.0% were born after their expected due date. Regarding fetal factors, the risk of antenatally unidentified SGA increased with increasing birth-weight centile (within the range of 0th–10th centile, adjusted odds increased by 1.21 (95% CI, 1.18–1.23) per one-centile increase ($P < 0.01$)) and was lowest for cases with a non-cephalic presentation at birth (aOR, 0.58 (95% CI, 0.46–0.73); $P < 0.01$) (Table 3).

Comparison of measures of ultrasound utilization

For the analysis in which only data from the last ultrasound scan were required, patterns of ultrasound use were investigated in the entire study sample of SGA pregnancies ($n \approx 15\,784$ across imputed datasets). For analyses which required data from earlier scans, births were excluded if they occurred at the one site that only provided data from the last scan (missing data on all other scans), leaving a total sample of ≈15 305 across imputed datasets. Patterns were also stratified by the presence or absence of indication for serial fetal ultrasound scans.

This required restriction to the sample with complete data on comorbidities and antenatal complications. Pregnancies were additionally excluded if care occurred in sites that did not provide any data on PAPP-A, leaving a total sample size of ≈7025 (Table 4).

Almost half of the pregnancies with unidentified SGA (47.1%) had no record of a fetal growth scan conducted at the site at which the women gave birth and 36.7% of women with unidentified SGA and an indication for serial screening did not undergo any scans. Over half (56.1%) of women who had SGA diagnosed antenatally required only one screening scan, meaning that EFW was below the 10th centile at the time of the first scan. Few women with identified SGA required more than three scans before SGA was identified. Regardless of the presence of indication for serial scans, a lower proportion of women with unidentified SGA underwent screening every ≤ 3 or 4 weeks compared to women with identified SGA; 42.7% of women with identified SGA underwent screening scans with high frequency (every 3 weeks or more often). Screening scans were generally commenced slightly later for women with unidentified SGA compared to those with identified SGA, with a lower proportion commencing scans before 31 weeks' gestation in the former group (46.3% *vs* 56.3%). The patterns for women with or without a documented indication for serial scans were similar to the unstratified results, although a higher proportion of women with a scan indication underwent scans, and conversely, more women without a documented scan indication did not undergo any scans. More women with a scan indication commenced their scans before 31 weeks (59.0% if SGA was unidentified, 70.0% if SGA was identified) (Table 4).

For pregnancies in which screening for SGA remained relevant (pregnancy ongoing and SGA had not yet been identified), the proportion of women undergoing any ultrasound scan during each gestational week starting from 26 weeks is presented in Figure 2. Screening ultrasound scans remained applicable to over 90% of women with unidentified SGA until 37 weeks, after which the proportion of women for whom it remained applicable decreased as the babies were born. For cases in which

Table 2 Association between maternal characteristics and unidentified small-for-gestational age (SGA), in pregnancies with complete data on maternal comorbidities and antenatal complications*

Characteristic	*Unidentified SGA (n ≈ 7532)*	*Identified SGA (n ≈ 1878)*	*OR (95% CI)*	*aOR (95% CI)*†	*Adjusted* P†
Maternal age					0.03
≤ 40 years	80.4	19.6	Ref	Ref	
> 40 years	74.1	25.9	0.69 (0.53–0.90)	0.74 (0.56–0.98)	
IMD quintile					0.47
1 (least deprived)	77.0	23.0	Ref	Ref	
2	78.8	21.2	1.10 (0.88–1.36)	0.97 (0.77–1.23)	
3	81.0	19.0	1.28 (1.05–1.54)	1.14 (0.92–1.41)	
4	81.2	18.8	1.27 (1.06–1.53)	1.10 (0.89–1.35)	
5 (most deprived)	79.7	20.3	1.14 (0.94–1.39)	1.05 (0.83–1.32)	
Race					< 0.01
White	80.9	19.1	Ref	Ref	
Black	80.1	19.9	0.95 (0.82–1.11)	0.95 (0.80–1.13)	
Asian	79.2	20.8	0.92 (0.81–1.04)	0.80 (0.69–0.93)	
Mixed	77.2	22.8	0.80 (0.54–1.19)	0.86 (0.57–1.31)	
Other	81.3	18.7	1.03 (0.85–1.24)	0.81 (0.65–1.00)	
BMI					0.04
< 18.5 kg/m^2	73.1	26.9	0.63 (0.51–0.79)	0.61 (0.48–0.76)	
18.5–24.9 kg/m^2	80.4	19.6	Ref	Ref	
25.0–29.9 kg/m^2	81.5	18.5	1.07 (0.94–1.22)	1.15 (1.01–1.32)	
30.0–34.9 kg/m^2	80.3	19.7	1.00 (0.83–1.21)	1.12 (0.91–1.38)	
35.0–39.9 kg/m^2	79.2	20.8	0.93 (0.69–1.24)	1.04 (0.77–1.42)	
≥ 40.0 kg/m^2	77.5	22.5	0.82 (0.54–1.26)	0.99 (0.63–1.54)	
Parity					0.15
0	80.9	19.1	Ref	Ref	
1	78.8	21.2	0.90 (0.80–1.02)	0.85 (0.74–0.97)	
2	80.4	19.6	1.00 (0.83–1.22)	0.99 (0.80–1.22)	
3	77.6	22.4	0.82 (0.62–1.09)	0.83 (0.62–1.12)	
≥ 4	80.9	19.1	0.99 (0.69–1.42)	1.00 (0.67–1.48)	
Smoking status					0.02
Non-smoker	80.5	19.5	Ref	Ref	
Smoker	77.2	22.8	0.82 (0.69–0.97)	0.79 (0.66–0.96)	

Data are given as %, unless stated otherwise. Data using multiply imputed datasets provide only percentages of characteristics of interest. *Except for pregnancy-associated plasma protein-A, for which data were missing in some cases. †Adjusted for all other demographic and clinical characteristics (age, index of socioeconomic deprivation (IMD) quintile, race, body mass index (BMI), parity and smoking status), birth-weight centile, maternal comorbidities and antenatal complications, and cluster site and trial phase. aOR, adjusted odds ratio; OR, odds ratio; Ref, reference.

SGA was identified antenatally, the gestational age of the initial diagnosis was distributed evenly throughout the third trimester. This was demonstrated by a linear decrease in the proportion of women receiving screening scans across the gestational ages. Amongst pregnancies in which SGA was not identified, screening scans were less common at all gestational ages when compared to women with identified SGA. Despite screening scans remaining relevant to a larger proportion of pregnancies at term amongst women with unidentified SGA *vs* those with identified SGA, fewer than 10% of remaining women underwent a scan during any week of gestation at term.

Women with unidentified SGA had an adjusted mean of 18.0 additional days between their last scan and delivery compared to women with identified SGA (28.2 *vs* 10.5 days; adjusted difference, 18.0 (95% CI, 17.2–18.8) days; $P < 0.001$); this is partly because many of the women with identified SGA underwent surveillance scans (no longer requiring screening) for diagnosed SGA. The mean duration between the last scan and birth increased with increasing gestational age at birth; pregnancies in which SGA was not identified had the last scan conducted 30.7 (SD, 21.7) days before birth if birth occurred at or after 39 + 0 weeks, and 18.7 (SD, 16.4) days before birth if it occurred between 37 + 0 and 38 + 6 weeks.

Of all SGA babies, 90.3% were born at term. The results of the analysis limited to these cases focusing on EFW and EFW centiles at the last ultrasound scan before birth compared with birth weight and birth-weight centiles are reported in Table 5. The 13.3% of unidentified SGA babies born within a week of the last growth scan had a mean EFW centile of 25.6 (SD, 14.0). The difference between EFW and birth-weight centiles in the unidentified-SGA group was 19.5 (SD, 13.8) centiles, with an adjusted mean difference in difference between centiles compared with the identified-SGA group of 19.0 (95% CI, 17.8–20.1) centiles ($P < 0.01$). The difference between EFW and birth weight in g expressed as a percentage of birth weight in the unidentified-SGA group was 13.5% (SD, 7.3%), with an adjusted mean difference in percentage difference compared with the identified-SGA group of 9.8% (95% CI, 9.0–10.6%) ($P < 0.01$). As the duration between the last growth ultrasound scan and birth increased, the centile difference in the identified-SGA group increased only marginally, although the difference between EFW at the time of scan and the actual birth weight a few weeks later increased, as expected. For pregnancies in which SGA was not identified antenatally, a different relationship was seen. For these pregnancies, as the duration between the last scan and birth increased, the difference between centiles increased, but the percentage

Table 3 Association of comorbidities and fetal characteristics with unidentified small-for-gestational age (SGA), in pregnancies with complete data on maternal complications and comorbidities*

Characteristic	*Unidentified SGA (n ≈ 7532)*	*Identified SGA (n ≈ 1878)*	*OR (95% CI)*	*aOR (95% CI)†*	*Adjusted* P†
Comorbidity					
No hypertension	80.4	19.6	Ref	Ref	
Hypertension	71.6	28.4	0.62 (0.45–0.86)	0.83 (0.59–1.17)	0.29
No diabetes	80.3	19.7	Ref	Ref	
Diabetes	69.3	30.7	0.51 (0.35–0.76)	0.52 (0.34–0.79)	< 0.01
Antenatal complication					
No pre-eclampsia	80.9	19.1	Ref	Ref	
Pre-eclampsia	60.4	39.6	0.34 (0.27–0.44)	0.40 (0.31–0.51)	< 0.01
No gestational hypertension	80.5	19.5	Ref	Ref	
Gestational hypertension	66.7	33.3	0.47 (0.34–0.63)	0.54 (0.39–0.74)	< 0.01
No GDM	80.6	19.4	Ref	Ref	
GDM	73.0	27.0	0.65 (0.52–0.80)	0.64 (0.51–0.80)	< 0.01
PAPP-A					< 0.01
< 0.300 MoM	57.3	42.7	0.38 (0.28–0.53)	0.45 (0.32–0.64)	
0.300–0.415 MoM	64.0	36.0	0.51 (0.39–0.66)	0.56 (0.43–0.75)	
> 0.415 MoM	77.8	22.2	Ref	Ref	
Indication for serial fetal scans					
No indication	82.8	17.2	Ref	Ref	
Any indication	72.0	28.0	0.53 (0.47–0.60)	0.56 (0.49–0.64)§	< 0.01
Neonatal presentation at birth					
Cephalic	81.4	18.6	Ref	Ref	
Non-cephalic	69.2	30.8	0.49 (0.39–0.61)	0.58 (0.46–0.73)	< 0.01
Birth-weight centile	5.4 ± 2.9	4.0 ± 2.8	1.20 (1.17–1.22)‡	1.21 (1.18–1.23)‡	< 0.01

Data are given as % or mean ± SD, unless stated otherwise. Data using multiply imputed datasets provide only percentages of characteristics of interest. *Available case data (except for data on pregnancy-associated plasma protein-A (PAPP-A), which were included even if missing). †Odds ratio (OR) for unidentified SGA, adjusted for all other demographic and clinical characteristics (age, index of socioeconomic deprivation (IMD) quintile, race, body mass index, parity and smoking status), birth-weight centile, maternal comorbidities and antenatal complications, and cluster site and trial phase. ‡Change in OR with one-centile increase (< 10th centile). §Adjusted only for IMD, parity, race and birth-weight centile (not for other characteristics that are included in this composite). aOR, adjusted odds ratio; GDM, gestational diabetes mellitus; MoM, multiples of the median; Ref, reference.

difference between EFW and birth weight decreased; thus, EFW measurements taken 4 weeks before birth were closer to the actual birth weight than EFW measurements taken within 1 week of birth (difference of −3.0% (SD, 9.2%) for scans 3–4 weeks before birth and 13.5% (SD, 7.3%) for scans within 1 week of birth).

Sensitivity analysis

On available-case sensitivity analysis, characteristics and comparisons for the included SGA pregnancies were broadly similar to the main analysis, with consistent point estimates for all studied characteristics and patterns of ultrasound use, except for pre-existing diabetes (aOR, 0.9 (95% CI, 0.5–1.5); $P = 0.64$), which was no longer associated with SGA detection status. Whilst there was a loss of statistical significance at $P < 0.05$ threshold, this is very likely to be due to loss in statistical power from the reduced sample size (Tables 1–4 in Appendix S1).

The sensitivity analysis was also conducted after restricting the sample to pregnancies with a recorded anomaly scan at the site of birth. Fewer women underwent

Table 4 Patterns of ultrasound use in all pregnancies with identified and those with unidentified small-for-gestational-age (SGA), overall and according to whether there was indication for serial fetal growth scans

	All SGA (n ≈ 15 784)		*Serial scan indication*		*No serial scan indication**	
Characteristic	*Unidentified SGA (n ≈ 12 416)*	*Identified SGA (n ≈ 3368)*	*Unidentified SGA (n ≈ 1591)*	*Identified SGA (n ≈ 619)*	*Unidentified SGA (n ≈ 3989)*	*Identified SGA (n ≈ 826)*
Screening scans performed (*n*)						
0	47.1	—	36.7	—	55.1	—
1	21.4	56.1	17.9	54.1	20.6	59.4
2	14.8	26.5	19.9	25.6	12.2	25.4
3	10.8	12.4	17.2	14.3	8.1	10.3
4	4.1	4.2	5.6	4.7	2.9	4.3
≥ 5	1.8	0.8	2.6	1.4	1.0	0.6
Interval between screening scans†						
≤ 3 weeks	14.5	42.7	14.2	43.1	15.1	42.8
4 weeks	14.0	30.0	12.2	26.2	13.3	25.9
> 4 weeks	71.6	27.3	73.6	30.7	71.6	31.3
GA at first scan (if scans conducted)						
< 31 + 0 weeks	46.3	56.3	59.0	70.0	42.3	47.3
31 + 0 to 33 + 6 weeks	15.6	13.7	14.8	11.9	15.6	16.1
34 + 0 to 36 + 6 weeks	27.4	19.7	20.3	13.0	26.2	22.5
≥ 37 + 0 weeks	10.7	10.3	5.9	5.1	15.9	14.2

Data are given as %. Data using multiply imputed datasets provide only percentages of characteristics of interest. Analysis according to presence of serial scan indication was restricted to sample with complete data on comorbidities and antenatal complications from sites that provided data on pregnancy-associated plasma protein-A (PAPP-A). *Includes records for which PAPP-A was not documented. †For pregnancies with at least two scans. GA, gestational age.

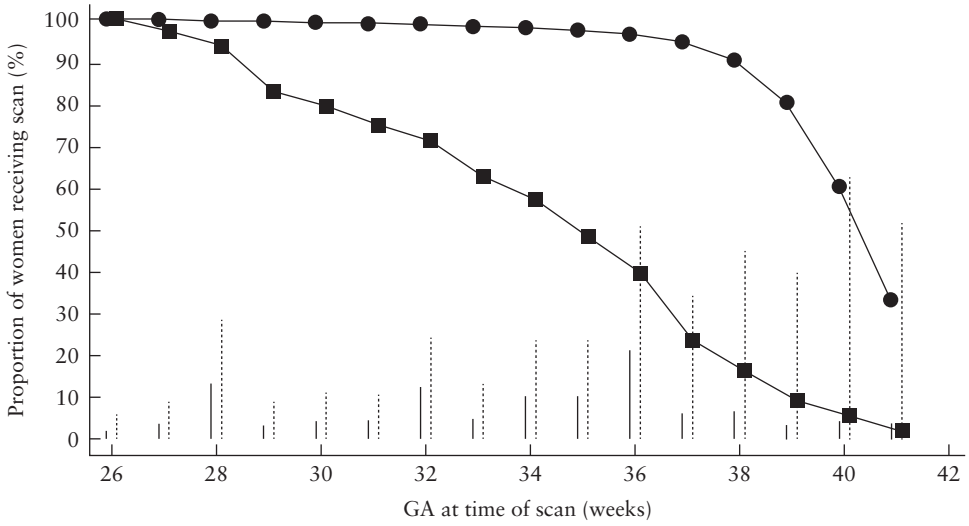

Figure 2 Proportion of women receiving a screening ultrasound scan for fetal growth (vertical lines), amongst the proportion in whom screening for small-for-gestational age (SGA) remains relevant (symbols), presented according to SGA detection status. ■, proportion for whom SGA screening remains relevant (SGA detected antenatally); ●, proportion for whom SGA screening remains relevant (SGA missed antenatally); ....., proportion scanned (SGA detected antenatally); ——, proportion scanned (SGA missed antenatally); GA, gestational age.

Table 5 Comparison of estimated fetal weight (EFW) at last ultrasound scan and birth weight, according to time between last scan and birth, in pregnancies with identified and those with unidentified small-for-gestational age (SGA) delivered at term

Parameter	*Unidentified SGA (n ≈ 5544)*	*Identified SGA (n ≈ 1525)*	*Unadjusted mean difference (95% CI)*	*Adjusted mean difference (95% CI)**	*Adjusted P**
Last scan within 1 week of birth					
EFW centile at last scan	25.6 ± 14.0	4.6 ± 2.9	20.9 (19.8–22.0)	20.6 (19.5–21.7)	< 0.01
Difference between EFW and birth-weight centiles	19.5 ± 13.8	0.2 ± 3.3	19.3 (18.2–20.4)	19.0 (17.8–20.1)	< 0.01
Percentage difference between EFW and birth weight	13.5 ± 7.3	2.4 ± 10.9	11.0 (10.1–12.0)	9.8 (9.0–10.6)	< 0.01
Last scan within 1–2 weeks of birth					
EFW centile at last scan	26.8 ± 14.1	5.3 ± 2.8	21.5 (19.8–23.1)	21.2 (19.5–22.8)	< 0.01
Difference between EFW and birth-weight centiles	21.0 ± 14.0	0.6 ± 3.4	20.3 (18.7–21.9)	20.0 (18.4–21.7)	< 0.01
Percentage difference between EFW and birth weight	10.9 ± 38.0	−2.6 ± 9.1	13.5 (9.1–17.9)	12.9 (8.5–17.3)	< 0.01
Last scan within 2–3 weeks of birth					
EFW centile at last scan	27.1 ± 14.1	5.4 ± 2.8	21.7 (19.9–23.5)	21.5 (19.6–23.3)	< 0.01
Difference between EFW and birth-weight centiles	21.0 ± 14.0	1.2 ± 3.6	19.8 (18.0–21.6)	19.7 (17.8–21.5)	< 0.01
Percentage difference between EFW and birth weight	3.2 ± 27.1	−8.1 ± 12.2	11.2 (7.7–14.8)	9.2 (5.6–12.8)	< 0.01
Last scan within 3–4 weeks of birth					
EFW centile at last scan	29.7 ± 15.0	5.6 ± 3.3	24.1 (21.6–26.6)	24.0 (21.4–26.6)	< 0.01
Difference between EFW and birth-weight centiles	24.0 ± 14.8	1.6 ± 4.2	22.3 (19.9–24.7)	22.1 (19.5–24.6)	< 0.01
Percentage difference between EFW and birth weight	−3.0 ± 9.2	−13.2 ± 27.2	10.2 (7.9–12.6)	5.6 (3.4–7.9)	< 0.01

Data are given as mean ± SD, unless stated otherwise. *Adjusted for cluster site and trial phase only.

a presumed anomaly scan at the cluster site in which they later gave birth in the unidentified-SGA group compared to the identified-SGA group (76.1% *vs* 90.8%). The rate of detection of SGA (24.4%) in this restricted sample was similar to that in the main analysis. Compared with the primary sample, the sample restricted to pregnancies with an anomaly scan showed similar findings (Tables 1 and 2 in Appendix S2), except that an additional association was found, whereby the risk of unidentified SGA was lower amongst women with pre-existing hypertension (aOR, 0.6 (95% CI, 0.4–0.9); $P < 0.01$). With regard to the patterns of ultrasound use, a lower proportion of women with unidentified SGA underwent no fetal growth scan after 24 + 0 weeks of pregnancy (36.6% of all women). All other findings were similar (Tables 3 and 4 in Appendix S2).

DISCUSSION

Summary of key findings

Overall, 78.7% of SGA cases were missed antenatally. Having no recorded indication for serial ultrasound increased the risk of missing SGA antenatally; 68.5% of all SGA pregnancies had no known indication. Almost half of pregnancies with unidentified SGA had no growth scan, despite one-third of them having an indication. Non-cephalic presentation also reduced the chance of unidentified SGA, but BMI of 25.0–29.9 kg/m^2 and less severe SGA increased the risk. For women with unidentified SGA who underwent growth scans, the last scan-to-birth interval widened with later birth, demonstrating policies to stop scanning at 36 weeks' gestation. EFW from scans conducted within a week before birth was overestimated by 10.3 centiles for all SGA term babies and by more amongst unidentified-SGA babies (19.5 centiles).

Interpretation of findings

Whilst we expected that having an indication for serial scans would increase SGA detection (demonstrating the application of national targeted screening)[29], it is less established that most SGA pregnancies have no risk factors. Such women are deprioritized and undergo less sensitive screening (fundal height measurement)[30,31], increasing their risk of unidentified SGA. Amongst women at low risk of SGA, serial scans also have low sensitivity, presenting a diagnostic challenge[12,13]. Furthermore, it is not clear whether the unidentified-SGA babies born to women with no SGA risk factors have the same risk of adverse outcome as SGA babies born to women with predisposing factors.

Over half of cases with unidentified SGA were born after 40 weeks of gestation, some of which had earlier growth scans demonstrating normal size. Unidentified SGA in this context can be explained by late-onset growth restriction, overestimated fetal weight, loss of fetal weight or a combination of these. Overestimated fetal weight has been reported previously in a meta-analysis[32], and fetal weight loss has been hypothesized in single- and multicenter cohort studies, which reported similar rates of SGA detection to those reported here[33,34].

The reduced risk of unidentified SGA in non-cephalic cases may be explained by incidental SGA identification when scanning for suspected non-cephalic presentation[35]. A UK report recommending universal late-pregnancy ultrasound screening for fetal presentation, but without simultaneous fetal growth assessment (as is often practiced), did not consider whether this will reduce SGA detection amongst non-cephalic babies[36].

Women with BMI of 25.0–29.9 kg/m^2 (and possibly with BMI of 30.0–34.9 kg/m^2) were at greater risk of unidentified SGA compared to those with healthy BMI. Fundal height measurement is affected by maternal BMI,

although current protocols[31,37–39] recommend serial ultrasound only for women with BMI above 35 kg/m^2. Given the considerable proportion of women with unidentified SGA who had BMI of 25.0–29.9 kg/m^2 (27.1%), research investigating methods to improve fetal weight estimation in this group is expected to have wide impact.

Strengths and limitations

To the best of our knowledge, this is the largest and most comprehensive study on this topic, suggesting novel targets to improve SGA screening[19,20,40]. The use of data from electronic patient records allowed inclusion of a large sample, but was limited by data quality and availability[24]. The analysis assessed detection amongst SGA neonates, although we are aware that FGR is better correlated with risk of perinatal morbidity and mortality and therefore may be a better screening target to reduce the rate of adverse outcome and limit iatrogenic harm. Nevertheless, detection of SGA is the end target of national and international guidelines on this topic[10], hence our decision to define our primary outcome in this way. Data were not available on some indications for serial fetal ultrasound in the UK[41,42], although the missing indicators were either rare (e.g. chronic kidney disease) or could have affected only the 42.2% of women with no known risk factor who were parous (no data on previous stillbirth or SGA pregnancy). Our assumption that women with no ultrasound record had no scans had little impact when tested on sensitivity analysis. The results are generalizable to maternity care settings in the UK and other countries that adopt similar selective ultrasound strategies for fetal growth[31,41].

Implication of findings

Given the proportion of women who underwent no serial scans despite having an indication, investigating missed cases of SGA is key to improving care quality. Maternity units in the DESiGN trial cited resource availability (including sonographer shortages) as a reason for incomplete concordance with national guidelines on SGA screening[43]. Economic evaluations assessing the strategy of offering serial ultrasound to women with less implemented indications, such as BMI 35–40 kg/m^2, are required to demonstrate the cost-effectiveness of recommended practice.

Further research is also required to assess alternative screening strategies for women without known risk factors for SGA. Whilst performing a single growth ultrasound scan has only low-to-moderate sensitivity in this group, the sensitivity improves with advancing gestation[30,32]. The optimal timing of a universally offered late scan and the effect of measuring the change in the EFW centile between two scans for women who have a one-off indication for a fetal scan (e.g. small fundal height measurement) are unknown. Policies to continue serial scans until birth have been introduced into common UK practice through the Saving Babies' Lives care bundle[29,44], but were not widely implemented in the studied maternity units. There is currently no published research studying the benefit of this resource-intense policy, except when part of complex interventions[45–47]. Studies of the accuracy of ultrasound assessment of EFW at term vary in their findings[48–51], but accuracy appears to be problematic; techniques are required to improve this strategy and other methods (e.g. biomarkers of placental function) that identify the fetus at risk of perinatal mortality.

Conclusions

The risk of antenatally unidentified SGA is greater in the absence of indication for serial ultrasound growth scans, and with BMI between 25.0–29.9 kg/m^2, less severe SGA and cephalic presentation. Two-thirds of pregnancies with SGA had no indication for serial growth scans, emphasizing the need to improve SGA screening in low-risk populations. Amongst those who underwent a scan, the EFW was generally overestimated, precluding SGA diagnosis.

Missed-case analysis should play an important role in quality improvement. Further research is needed to determine how SGA detection can be improved for women who are overweight or without classic risk factors for SGA and identify which of the unidentified-SGA cases are most at risk of adverse outcome.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Available-case sensitivity analysis

Appendix S2 Sensitivity analysis for women with a recorded anomaly scan