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

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.26091

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Short title: Characteristics associated with unidentified SGA

Keywords: Small-for-gestational age, fetal growth, antenatal screening, ultrasound patterns, risk factors, estimated fetal weight, maternal characteristics

CONTRIBUTION

What are the novel findings of this work?

Pregnancies with unidentified small-for-gestational age (SGA) were less likely to have serial scan indications, and more likely to have body mass index 25.0-29.9 kg/m^2, less severe SGA and cephalic presentation. Two-thirds of SGA pregnancies had no serial scan indication, emphasizing the importance of accurate screening strategies in low-risk women.

What are the clinical implications of this work?

Unidentified SGA is more likely amongst women without scan indications or with overweight BMI. 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 antenatally unidentified SGA, compared to those in which it is identified, to understand how to better design interventions that improve antenatal SGA identification.

Methods: A prospective cohort study of singleton, non-anomalous, small for gestational age (SGA, birthweight<10th centile) babies born after 24+0 gestational weeks, from 13 UK sites, collected for the baseline period and control arm of the DESiGN trial. We define pregnancies with antenatally unidentified SGA where there was no scan or a final scan with estimated fetal weight, EFW, at 10th centile or above; and as identified SGA if EFW was below 10th centile at 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, ultrasound frequency, duration between the last scan and the birth, absolute centile difference between the last scan and the birth) were described and associations with missed SGA were also studied by unadjusted and adjusted logistic regression but stratified by presence of indications for serial ultrasound.

Results: Of the 15,784 SGA babies included, SGA was not identified antenatally in 78.7%. Of pregnancies with unidentified SGA, 47.1% had no recorded growth scan. Amongst 9,410 pregnancies with complete data on key maternal co-morbidities and antenatal complications, the risk of unidentified SGA was lower for women with any indication for serial scans (aOR 0.56, 95% CI: 0.49-0.64), Asian ethnicity (aOR 0.80 compared to white, 95% CI: 0.69-0.93) and non-cephalic presentation (aOR 0.58, 95% CI: 0.46-0.73). The risk of unidentified SGA was highest among women with BMI 25.0-29.9 kg/m^2 (aOR 1.15 compared to 18.5-24.9 kg/m^2, 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 identified SGA, those with unidentified SGA had fetuses of higher SGA birthweight centile (adjusted mean difference 1.21, 95% CI: 1.18-1.23). 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 EFW: birthweight centile difference of +19.5 (SD: 13.8) for unidentified SGA babies and +0.2 (SD: 3.3) for identified SGA babies (adjusted difference 19.0, CI: 17.8-20.1).

Conclusions: Unidentified SGA was more common amongst women without indications for serial ultrasound, cephalic presentation, BMI 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 ultrasound scans for term pregnancies.

INTRODUCTION

The reduction of stillbirth and perinatal death is an international priority.[1] Between 30-50% of stillborn babies are small for gestational age (SGA, birthweight <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 should be targeted to reduce 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 rate of detection of SGA under 50%.[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, but without consequential increase in false positive diagnoses, requires an understanding of the characteristics of women and babies in whom SGA is not currently identified antenatally. Previous studies have found FGR was more likely to be detected amongst multiparous women (particularly those with a previous FGR baby), of lower BMI, 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 AC>10th centile) or for women cared for in low-risk midwifery-led settings.[20] However, clinical characteristics included in either study were limited.

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

METHODS

Study design

This prospective cohort study was conducted using data on pregnancies and births collected for the DESiGN trial. DESiGN was a UK randomized cluster control trial conducted between 05/11/2016-28/3/2019 that compared the clinical effectiveness of the Growth Assessment Protocol (GAP) to standard care on the rate of antenatal detection of SGA, finding no difference between interventions on the primary outcome. Detailed descriptions of the trial and data collection methods have been previously published.[21-23]

For this analysis, only pregnancies in which the baby was born SGA (defined as birthweight below the 10th centile for gestational age on population reference charts)[24] after 24^{+0} gestational weeks and that were not exposed to the intervention were 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 data on ultrasound were missing during an entire trial phase at a cluster site (affecting data from two clusters) were also excluded.

This study has been reported according to the recommendations of the STROBE statement for observational studies.[25]

Defining antenatally identified and unidentified cases of SGA

Antenatally unidentified SGA was defined as pregnancies in which the baby was diagnosed as being SGA at birth (birthweight <10th centile on population birthweight charts[24]), but for whom there was no evidence that an antenatal ultrasound diagnosis had been made i.e., the woman had not received growth scans, or the EFW at the last fetal growth scan (defined as any scan with fetal biometry conducted after 24^{+0} weeks') was above the 10th centile for gestational age. Identified SGA was defined in pregnancies in which an antenatal diagnosis of SGA had been correctly made i.e., the EFW at the last fetal growth ultrasound was below the 10th centile for gestational age. This outcome was chosen because clinical guidelines on the management of pregnancies with suspected SGA currently commonly apply the EFW<10th centile threshold, and decisions regarding timing and mode of birth are largely driven by the EFW at the last scan. The EFWs were assessed against Hadlock fetal growth charts.[26]

Exposures

The maternal or fetal characteristics studied were maternal age, index of socioeconomic deprivation quintile, ethnicity (Black, white, Asian, mixed, other), BMI (in kg/m^2: <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0+), parity (0, 1, 2, 3, 4+), smoking, maternal co-morbidities (pre-existing hypertension or diabetes), antenatal complications (pre-eclampsia, gestational hypertension, gestational diabetes [GDM]), low placenta-associated plasma protein A (PAPP-A, <0.3 MoM, 0.3-0.415 MoM, >0.415 MoM), non-cephalic presentation at birth, birthweight centile (continuous or <3rd centile, 3rd-5th centile, 5-10th 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 (age>40years, BMI≥35 kg/m^2, smoking, any of the above maternal co-morbidities or antenatal complications, PAPP-A<0.415 MoM). The maternal co-morbidities and antenatal complications were selected 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 we had access to data.

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

The patterns of ultrasound scans studied were: gestational age at the time of first fetal growth scan, frequency of serial screening scans (mean and categorical – 3-weekly, 4-weekly, less than 4-weekly), duration from the last (screening or surveillance) scan until birth, difference between the EFW at the last scan and the birthweight expressed in terms of absolute centiles and as weight difference as a percentage of the birthweight. The calculation of mean screening frequency accounted for different gestations at the time of: commencing serial screening scans (e.g., because of indications that arise later in pregnancy), antenatal diagnoses of SGA that stop the screening period, and birth itself, by dividing the period from the gestation of the first scan until the gestation of the last screening scan, by n minus 1 (n=number of

screening scans performed). For this, 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.[23] The primary analysis of factors associated with SGA detection status used imputed data on demographics and growth status, but co-morbidities, antenatal complications and fetal presentation were not imputed and were therefore analyzed on an available case basis. Where multiple imputation was used only percentages and not numbers are provided (except to approximate the total number of included births for each analysis), since frequencies are averaged across 10 imputed datasets. Since 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 was included as an exposure category, and in addition to the principles above, PAPP-A was only studied in clusters that provided data on it. For the study of ultrasound patterns, it was assumed that pregnancies without a record of a fetal growth scan had not had a scan (a sensitivity analysis, described below, was conducted to test the impact of this assumption). Rubin's rules were used for analysis of imputed data.[27]

Statistical analysis

The number and proportion of pregnancies in which the baby was SGA at birth, and in which this was antenatally diagnosed, were calculated.

Characteristics of pregnancies in which SGA was not identified were summarized using descriptive statistics (number and percentage, mean and standard deviation as appropriate). Characteristics of pregnancies with unidentified SGA were then compared to 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, ethnicity, BMI, parity and smoking status), the allocated birthweight centile of the neonate, and the maternal co-morbidities and antenatal complications. Since the data were collected from a cluster trial population, all models were also adjusted by the cluster site and the trial phase, to account for clustering and temporal changes.

Patterns of screening ultrasound utilization were also summarized using descriptive statistics, unadjusted and adjusted comparisons as described above 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 without indications for serial fetal ultrasound scans, the comparisons were stratified by the presence or absence of an indication; this available-case analysis was conducted amongst the sample of women who had complete information on presence or absence of co-morbidities and antenatal complications, with antenatal care at sites that provided data on PAPP-A.

Sensitivity analyses

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 (N= 5,307 with complete data on co-morbidities and antenatal complications of which SGA was not identified in 4,129 (77.8%); larger sample with complete data at least on SGA status for analysis of ultrasound patterns: 15,247 with unidentified SGA in 11,897, 78.0%). The second sensitivity analysis used only pregnancies (N=12,122; 9,164 (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 received one at that site or elsewhere.

RESULTS

Of the 169,724 pregnancies included in the control arm of the DESIGN RCT, 9.3% (n=15,784) were SGA at birth and included in the main analyses of this paper. 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.[22] Of these, SGA was not identified antenatally in 12,416 (78.7%). Following exclusion of pregnancies with missing data on maternal co-morbidities and antenatal complications, 9,410 pregnancies were available for assessment of maternal and fetal characteristics associated with unidentified SGA (Figure 1).

Factors associated with unidentified SGA

The characteristics of the included women and babies are summarized in Table 1 by SGA detection status. Amongst women in whom SGA was unidentified there was a lower proportion of age 40 years or over (3.7% vs 5.2%), underweight BMI (5.0% vs 7.5%), smoking (8.7% vs 10.4%) or any co-morbidity (chronic hypertension 1.9% vs 3.05; 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 an SGA baby 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 than unidentified SGA (42.8% vs 28.5%, p<0.01).

Unadjusted and adjusted comparisons of demographic characteristics and co-morbidities or antenatal complications between pregnancies in which SGA was not identified antenatally, or antenatally identified, are presented in Tables 2 and 3. Following mutual adjustment for other factors, the risk of unidentified SGA was lower for: women with age over 40 years (aOR 0.74, CI: 0.56-0.98, p=0.03), women of Asian relative to white ethnicity (aOR 0.80, CI: 0.69-0.93, global ethnicity p<0.01), smokers (aOR 0.79, CI: 0.66-0.96, p=0.02), those with BMI <18.5 kg/m^2 relative to BMI of 18.5-24.9 kg/m^2 (aOR 0.61, CI: 0.48-0.76, global BMI p=0.04), pre-existing (aOR 0.52, CI: 0.34-0.79, p<0.01) or gestational diabetes (aOR 0.64, CI: 0.51-0.80, p<0.01), gestational hypertension (aOR 0.54, CI: 0.39-0.74, p<0.01), pre-eclampsia (aOR 0.40, CI: 0.31-0.51, p<0.01) or low PAPP-A (aOR 0.45, CI: 0.32-0.64, p<0.01 for <0.3 MoM), or any indication for serial scans (composite aOR: 0.56, CI: 0.49-0.64, p<0.01). Relative to women with BMI 18.5-24.9 kg/m^2, risk of missed SGA was higher for women with BMI 25.0-29.9 kg/m^2 (aOR 1.15, CI: 1.01-1.32) and possibly BMI 30.0-34.9 kg/m2 (aOR 1.12, CI: 0.91-

1.38, global BMI p=0.04). An association was not observed for higher BMI categories, although these are limited by small numbers.

Overall, 9.7% of SGA babies were born preterm (<37 completed weeks' gestation). Compared to neonates in whom SGA was identified antenatally, neonates in whom SGA was not identified antenatally were less likely to be born prior to 39 weeks' gestation, including at early term, preterm and extreme preterm gestations, and were more likely to be born after 39 weeks' gestation. Of babies 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 birthweight centile (within the range 0-10th, aOR increase was 1.21 per one centile increase, CI: 1.18-1.23, p<0.01) and lowest for babies with a non-cephalic presentation at birth (aOR 0.58, CI: 0.46-0.73, p<0.01), see Table 3.

Comparing measures of ultrasound utilization between cases and controls

Patterns of ultrasound use were first investigated amongst the entire study sample of SGA pregnancies (n≈15,784 across imputed datasets) but with the exclusion of births occurring at 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 an indication for serial fetal ultrasound scans; this required restriction to the sample with complete data on co-morbidities 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 ≈7,025 (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 an indication for serial screening scans received none, despite having that indication. Over half (56.1%) of women who had SGA diagnosed antenatally required only one screening scan, meaning that the EFW was below the 10th centile at the time of the first scan. Very few women who had identified SGA required more than 3 scans before this was identified. Regardless of the presence of indications for serial scans, a lower proportion of women with unidentified SGA received 3-weekly or 4-weekly scans than women with identified SGA; the majority of women with identified SGA had received a higher frequency of screening scans (3-weekly 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' (46.3% vs 56.3%). The patterns for women with a documented indication for serial scans were similar, although a higher proportion of women with a scan indication received scans, and conversely, more women without a documented scan indication received none. 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 receiving 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. Where SGA was identified antenatally, the gestational age of the initial diagnosis was evenly distributed 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 gestations than amongst women with identified SGA. Despite screening scans remaining relevant to a larger proportion of pregnancies at term amongst women with unidentified SGA than identified SGA, less than 10% of remaining women received 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 their birth compared to women with identified SGA (28.2 days vs. 10.5 days, adjusted difference 18.0 days, CI: 17.2-18.8, $p<0.001$); this is partly because many of the women with identified SGA were receiving surveillance scans (no longer requiring screening) for diagnosed SGA. The duration between the last scan and the birth increased with increasing gestational age at birth; pregnancies in which SGA was not identified had the last scan conducted 30.7 days (SD 21.7) before the birth if it occurred at or after 39^{+0} weeks' gestation, or 18.7 (SD 16.4) days prior to birth if birth occurred between 37^{+0} – 38^{+6} weeks of gestation.

Of all SGA babies, 90.3% were born at term. The results of an analysis limited to these babies describing the EFWs and their centiles at the last ultrasound scan before birth, compared to the birthweights and birthweight 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), this equated to a difference between the EFW and birthweight centile of +19.5 (SD: 13.8,with an adjusted difference in difference when compared to identified SGA babies of

+19.0, CI: 17.8-20.1, p<0.001) and a difference in EFW and birthweight (grams) expressed as a percentage of the birthweight of +13.5% (SD: 7.3%with adjusted difference in difference compared to identified SGA babies of 9.8%, CI: 9.0-10.6%, p<0.001). As the duration between the last growth ultrasound and the birth increased, the centile difference for babies with identified SGA remained similar, although the difference between the EFW at the time of scan and the birthweight a few weeks later increased, as is expected. For pregnancies in whom SGA was not identified antenatally, a different relationship was seen. For these pregnancies, as the duration between the last scan and the birth increased, the difference between centiles increased, but the percentage difference between EFW and birthweight decreased so that EFW measurements taken 4 weeks before birth were closer to the actual birthweight than EFW measurements taken within one week of birth (-3.0%, SD: 9.2% difference for scans 4 weeks before birth, 13.5%, SD: 7.3% for scans within 1 week of birth).

Sensitivity analyses

Available case sensitivity analysis

The characteristics and comparisons for the included women and babies with SGA pregnancies were broadly similar to the main analysis in the available case 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 a loss in statistical power from the reduced sample size (Tables A-D, Appendix S1).

Restricting the sample to pregnancies with a record of an anomaly scan at the site of birth

Fewer women with unidentified SGA had received a presumed anomaly scan at the cluster site in which they later gave birth (76.1% versus 90.8% for women with identified SGA). The rate of detection of SGA (24.4%) in this restricted sample was similar to that in the main analysis. Compared to the primary sample, the sample restricted to pregnancies with an anomaly scan showed very similar findings (Tables A-B, Appendix S2) except that an additional association was found: 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 regards to the patterns of ultrasound use, a lower proportion of women with unidentified SGA receive no fetal growth

scan after 24+0 weeks of pregnancy (36.6% of all women). All other findings were similar (Tables C-D, Appendix S2).

DISCUSSION

Summary of the key findings

Overall, 78.7% of SGA was 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 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 received growth scans, the last scan to birth interval widened with later birth, demonstrating policies to stop scanning at 36 weeks. The 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.

Interpretation of the findings

Whilst we expected that having an indication for serial scans would increase SGA detection (demonstrating the application of national targeted screening),[28] it is less established that most pregnancies of SGA babies have no risk factors. Such women are deprioritized and receive less sensitive screening (fundal height measurement),[29, 30] 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 outcomes as SGA babies born to women with pathological factors.

Over half of babies with unidentified SGA were born after 40 weeks', some of whom had earlier growth scans demonstrating normal size. Unidentified SGA in this context can either be explained by late onset growth restriction, overestimated fetal weight, loss of fetal weight or a combination of these. Overestimated fetal weight has also previously been demonstrated by meta-analysis,[31] and fetal weight loss has been hypothesized from recent London and multicenter cohorts (reporting similar rates of SGA detection to those reported here).[32 33]

The reduced risk of unidentified SGA for non-cephalic babies may be explained by incidental SGA identification when scanning for suspected non-cephalic presentation.[34] A UK report recommending universal late pregnancy ultrasound screening for fetal presentation but

without simultaneous fetal growth assessment (as is often practiced) does not consider whether this will reduce SGA detection amongst non-cephalic babies[35] .

Women with overweight BMI (and possibly with BMI 30-34.9 kg/m2 category) were at greater risk of unidentified SGA compared to those with 'healthy' BMI. Fundal height measurement is affected by maternal BMI, although current protocols only recommend serial ultrasound for women with BMI above 35 kg/m^2.[30, 36-38] Given the proportion of women with BMI of 25-30 kg/m^2 and unidentified SGA (26.4%), researching 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 of this topic, suggesting novel targets to improve SGA screening.[19, 20, 39] Use of data from electronic patient records allowed inclusion of a large sample, but was limited by data quality and availability.[23] The analysis assessed detection amongst SGA babies, 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 adverse outcomes 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,[40, 41] although the missing indicators are either rare (e.g. chronic kidney disease) or could only have affected the 42.2% of women with no known risk factor who were multiparous (no data previous stillbirth or SGA baby). Our assumption that women with no ultrasound record had no scans had little impact when tested by sensitivity analyses. The results are generalizable to maternity care settings in the UK and other countries that adopt similar selective ultrasound strategies for fetal growth.[30, 40]

Implication of the findings

Given the proportion of women who received 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.[42] Economic evaluations assessing offer of serial ultrasound to women with less implemented indications (e.g., BMI 35-40 kg/m^2), are required to demonstrate cost-effectiveness of recommended practice.

Further research is also required to assess alternative screening strategies for women without known risk factors for SGA. Whilst conduct of a single growth ultrasound has only low to moderate sensitivity in this group, the sensitivity improves with advancing gestation.[29, 31] The optimal timing of a universally-offered late scan, or 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,[28, 43] 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.[44-46] Studies of the accuracy of ultrasound assessment of EFW at term vary in their findings,[47-50] but accuracy appears to be problematic; techniques are required to improve both this, or other methods (e.g. biomarkers of placental function) that identify the fetus at risk of perinatal mortality.

Conclusion

The risk of antenatally unidentified SGA is greater in the absence of indications for serial growth scans, with BMI between 25.0-29.9 kg/m^2, less severe SGA or 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 received 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 also to identify which of the unidentified SGA cases are most at risk of adverse outcomes.

ACKNOWLEDGMENTS

We wish to thank the other members of the DESiGN Trial Team: Kirstie Coxon, Andrew Healey, Donald Peebles, Baskaran Thilaganathan, Neil Marlow and Lesley McCowan, all of whom were co-investigators of the DESiGN trial and contributed to the design, conduct and reporting of the primary trial and the main secondary analyses. We would also like to thank the members of the DESiGN Collaborative Group (site principal investigators, GAP clinical leads and clinicians or IT professionals who assisted with data collection) all of whom have been named in previous publications.[22]

Disclosure

DAL has received support from Medtronic Ltd and Roche Diagnostics for research unrelated to that presented here.

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FIGURE LEGENDS

Figure 1: Construction of the study population (imputed data).

Figure 2: Proportion of women receiving a screening ultrasound for fetal growth, amongst the proportion in whom screening for SGA remains relevant, presented by SGA detection status.

Table 1 - Maternal and perinatal characteristics amongst pregnancies in which the small-for-gestational-age (SGA) fetus was antenatally unidentified or identified*

		Unidentified SGA (n≈7,532)	Identified SGA (n≈1,878)
Age (years)	**Mean (SD)**	30.5 (5.5)	30.9 (5.7)
	≤40y (%)	96.3%	94.8%
	>40y (%)	3.7%	5.2%
Index of multiple deprivation (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%
Ethnicity, %	**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)	**Mean (SD)**	25.0 (5.2)	24.8 (5.6)
	<18.5 (%)	5.0%	7.5%
	18.5-24.9 (%)	52.9%	52.2%
	25.0-29.9 (%)	27.1%	25.0%
	30.0-34.9 (%)	10.0%	9.9%
	35.0-39.9 (%)	3.4%	3.6%
	≥40.0 (%)	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 or above	2.5%	2.4%
Smoking status %	**Smoker**	8.7%	10.4%
Co-morbidities, %	**Hypertension**	1.9%	3.0%
	Diabetes	1.2%	2.1%
Antenatal complications, %	**Pre-eclampsia**	2.6%	6.9%
	Gestational hypertension	1.8%	3.6%
	Gestational diabetes	4.6%	6.8%
PAPP-A, %	**<0.300MoM**	1.6%	4.6%
	0.3-0.415MoM	3.0%	6.6%
	Missing data	49.8%	38.7%
Any indication for serial fetal scans,† %	**Any indication**	28.5%	42.8%
Neonatal presentation at birth, %	**Cephalic**	95.3%	91.2%
Gestational age at birth (weeks), %	**Mean (SD)**	37.7 (3.0)	39.8 (2.4)
	<28^{+0}	0.8%	1.9%
	28^{+0} – 33^{+6}	1.8%	8.0%
	34^{+0} – 36^{+6}	3.3%	15.2%
	37^{+0} – 37^{+6}	4.4%	15.3%
	38^{+0} – 38^{+6}	9.4%	19.8%
	39^{+0} – 39^{+6}	19.3%	17.6%
	40^{+0} or above	61.0%	22.2%
Birthweight centile‡	**Mean (SD)**	5.4 (2.9)	4.0 (2.8)
	<3rd centile (%)	24.9%	43.5%
	3rd – 5th centile (%)	18.7%	20.9%
	5th-10th centile (%)	56.5%	35.5%

*Data using multiply imputed datasets provides only percentages of characteristics of interest. Previous reports have reported demographic characteristics of the trial population.[22]

Table 2 - Association of maternal characteristics with unidentified small-for-gestational age (SGA)*

		Unidentified SGA (n≈7,532, 80.2%)	Identified SGA (n≈1,878, 19.8%)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Adjusted† p value
Age, %	**≤40y (%)**	80.4%	19.6%	Ref	Ref	0.03
	>40y (%)	74.1%	25.9%	0.69 (0.53-0.90)	0.74 (0.56-0.98)	
Index of multiple deprivation quintile (IMD), %	**1=least deprived**	77.0%	23.0%	Ref	Ref	0.47
	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)	
Ethnicity, %	**White**	80.9%	19.1%	Ref	Ref	<0.01
	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 (kg/m^2)	**<18.5 (%)**	73.1%	26.9%	0.63 (0.51-0.79)	0.61 (0.48-0.76)	0.04
	18.5-24.9 (%)	80.4%	19.6%	Ref	Ref	
	25.0-29.9 (%)	81.5%	18.5%	1.07 (0.94-1.22)	1.15 (1.01-1.32)	
	30.0-34.9 (%)	80.3%	19.7%	1.00 (0.83-1.21)	1.12 (0.91-1.38)	
	35.0-39.9 (%)	79.2%	20.8%	0.93 (0.69-1.24)	1.04 (0.77-1.42)	
	≥40.0 (%)	77.5%	22.5%	0.82 (0.54-1.26)	0.99 (0.63-1.54)	
Parity, %	**0**	80.9%	19.1%	Ref	Ref	0.15
	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 or above	80.9%	19.1%	0.99 (0.69-1.42)	1.00 (0.67-1.48)	
Smoking, status %	**Non-smoker**	80.5%	19.5%	Ref	Ref	Ref
	Smoker	77.2%	22.8%	0.82 (0.69-0.97)	0.79 (0.66-0.96)	0.02

***** Data using multiply imputed datasets provides only percentages of characteristics of interest.

† Adjusted for all other demographic and clinical characteristics (age, index of socioeconomic deprivation quintile, ethnicity, BMI, parity and smoking status), the allocated birthweight centile of the neonate, the maternal co-morbidities and antenatal complications and cluster site and the trial phase.

Table 3 – Association of co-morbidities and fetal characteristics with unidentified small-for-gestational age (SGA)

		Unidentified SGA (n≈7,532, 80.2%)	Identified SGA (n≈1,878, 19.8%)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Adjusted† p value
Co-morbidities, %	**No hypertension**	80.4%	19.6%	Ref	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	Ref
	Diabetes	69.3%	30.7%	0.51 (0.35-0.76)	0.52 (0.34-0.79)	<0.01
Antenatal complications, %	**No pre-eclampsia**	80.9%	19.1%	Ref	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	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	Ref
	GDM	73.0%	27.0%	0.65 (0.52-0.80)	0.64 (0.51-0.80)	<0.01
PAPP-A, %	**<0.300MoM**	57.3%	42.7%	0.38 (0.28-0.53)	0.45 (0.32-0.64)	<0.01
	0.3-0.415MoM	64.0%	36.0%	0.51 (0.39-0.66)	0.56 (0.43-0.75)	<0.01
	>0.415MoM	77.8%	22.2%	Ref	Ref	Ref
Indication for serial fetal scans, * %	**No indication**	82.8%	17.2%	Ref	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	Ref
	Non-cephalic	69.2%	30.8%	0.49 (0.39-0.61)	0.58 (0.46-0.73)	<0.01
Birthweight centile	**Mean (SD)**	5.4 (2.9)	4.0 (2.8)	1.20§ (1.17-1.22)	1.21§ (1.18-1.23)	<0.01

*Available case data (except for data on PAPP-A, which was included even if missing).

†OR for unidentified SGA, adjusted for all other demographic and clinical characteristics (age, index of socioeconomic deprivation quintile, ethnicity, BMI, parity and smoking status), the allocated birthweight centile of the neonate, the maternal co-morbidities and antenatal complications and cluster site and the trial phase.

‡Adjusted only for IMD, parity, ethnicity, and allocated birthweight centile (not for other adjustment characteristics which are included in this composite).

§ Change in OR with a one centile increase (<10^{th} centile).

Table 4 - Patterns of ultrasound use for all small-for-gestational-age (SGA) pregnancies, stratified by presence or absence of a recorded indication for serial fetal growth scans*

		All SGA (n≈15,784)		SGA with serial scan indication		SGA with no recorded serial scan indication†	
		Unidentified SGA (n≈12,416)	Identified SGA (n≈3,368)	Unidentified SGA (n≈1,591)	Identified SGA (n≈619)	Unidentified SGA (n≈3,989)	Identified SGA (n≈826)
Number of screening scans received, %	**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%
Screening scan frequency for pregnancies with at least two scans:	**≤3-weekly**	14.5%	42.7%	14.2%	43.1%	15.1%	42.8%
	4-weekly	14.0%	30.0%	12.2%	26.2%	13.3%	25.9%
	>4-weekly	71.6%	27.3%	73.6%	30.7%	71.6%	31.3%
Gestation at the time of the first scan, if scans conducted, %	**$<31^{+0}$**	46.3%	56.3%	59.0%	70.0%	42.3%	47.3%
	31^{+0}-33^{+6}	15.6%	13.7%	14.8%	11.9%	15.6%	16.1%
	34^{+0}-36^{+6}	27.4%	19.7%	20.3%	13.0%	26.2%	22.5%
	$\geq 37^{+0}$	10.7%	10.3%	5.9%	5.1%	15.9%	14.2%

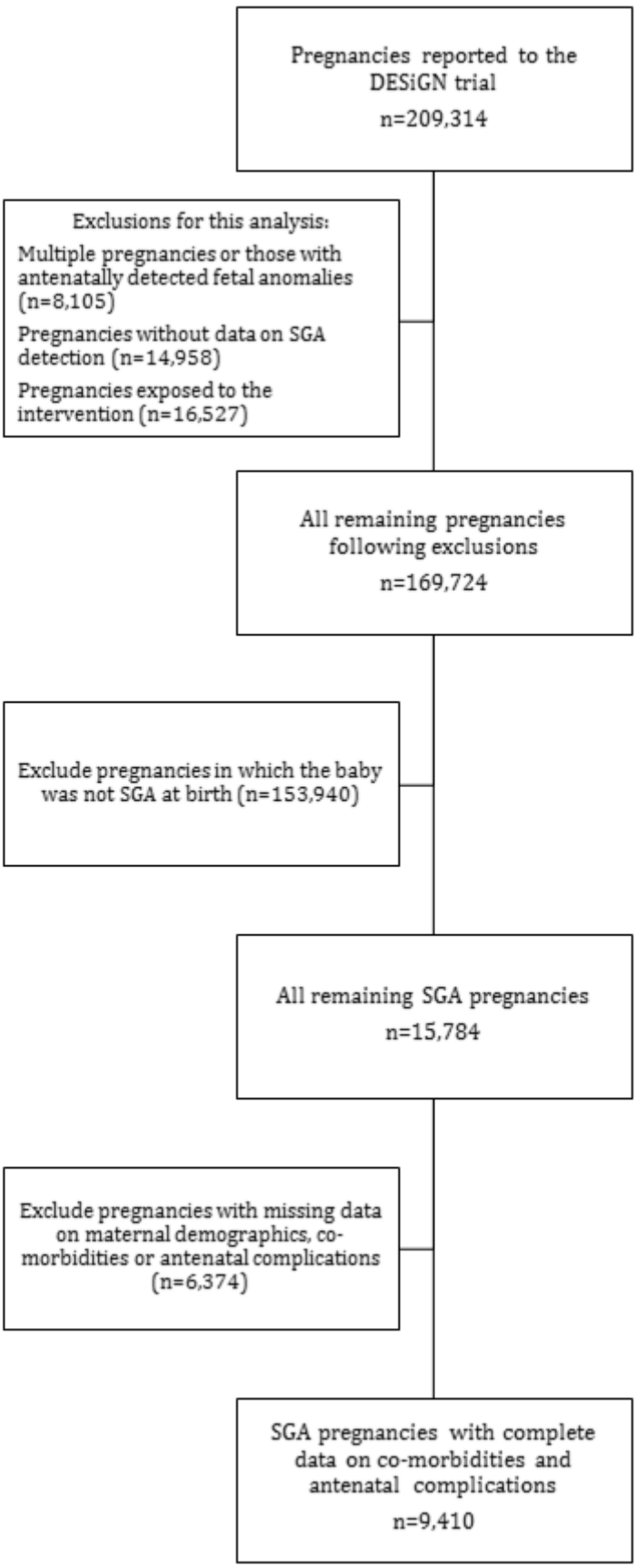
Data using multiply imputed datasets provides only percentages of characteristics of interest.

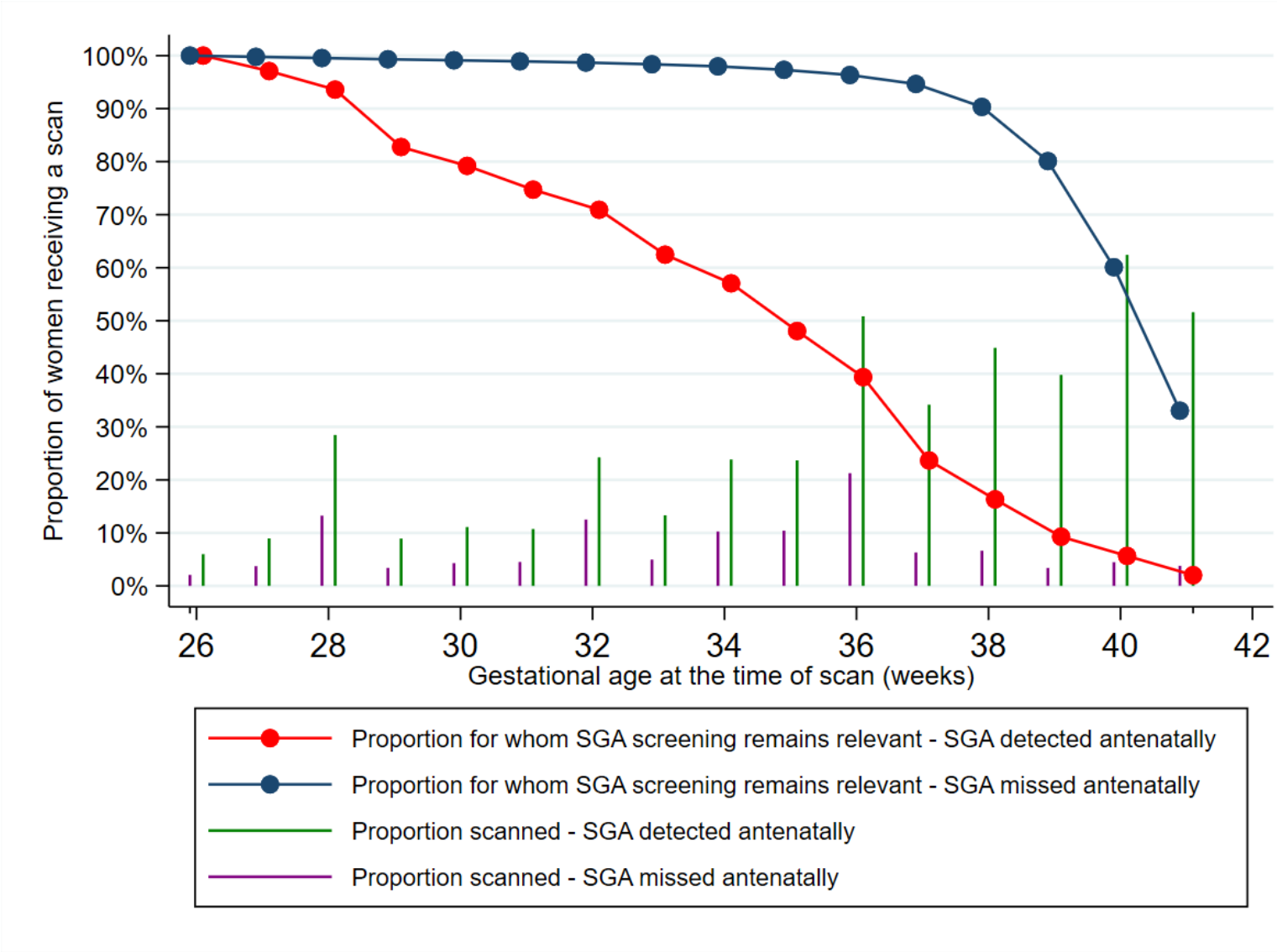
† Includes records for which PAPP-A was not documented.

Table 5 - Comparison of estimated fetal weight at the last ultrasound scan and the birthweight, including their centiles, for small-for-gestational-age (SGA) babies born at term

	Unidentified SGA	Identified SGA	Unadjusted mean diff (95% CI)	Adjusted mean diff*(95% CI)	Adjusted* p value
If scan within 1 week:					
EFW centile at last scan, mean (SD)	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 birthweight centiles, mean (SD)	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 birthweight, mean (SD)	13.5% (7.3%)	2.4% (10.9%)	11.0% (10.1-12.0)	9.8% (9.0-10.6)	<0.01
If scan within 1-2 weeks:					
EFW centile at last scan, mean (SD)	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 birthweight centiles, mean (SD)	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 birthweight, mean (SD)	10.9% (38.0%)	-2.6% (9.1%)	13.5% (9.1-17.9)	12.9% (8.5-17.3)	<0.01
If scan within 2-3 weeks:					
EFW centile at last scan, mean (SD)	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 birthweight centiles, mean (SD)	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 birthweight, mean (SD)	3.2% (27.1%)	-8.1% (12.2%)	11.2% (7.7-14.8)	9.2% (5.6-12.8)	<0.01
If scan within 3-4 weeks:					
EFW centile at last scan, mean (SD)	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 birthweight centiles, mean (SD)	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 birthweight, mean (SD)	-3.0% (9.2%)	-13.2% (27.2%)	10.2% (7.9-12.6)	5.6% (3.4-7.9)	<0.01

*Adjusted for cluster site and trial phase only.





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