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RANDOMISED CONTROLLED TRIAL

Antenatal detection of large-for-gestational-age fetuses following implementation of the Growth Assessment Protocol: secondary analysis of a randomised control trial

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Abstract

Objective: To determine whether the Growth Assessment Protocol (GAP) affects the antenatal detection of large for gestational age (LGA) or maternal and perinatal outcomes amongst LGA babies.

Design: Secondary analysis of a pragmatic open randomised cluster control trial comparing the GAP with standard care.

Setting: Eleven UK maternity units.

Population: Pregnant women and their LGA babies born at $\geq 36^{+0}$ weeks of gestation.

Methods: Clusters were randomly allocated to GAP implementation or standard care. Data were collected from electronic patient records. Trial arms were compared using summary statistics, with unadjusted and adjusted (two-stage cluster summary approach) differences.

Clinical trial registration: ISRCTN67698474 (https://doi.org/10.1186/ISRCTN67698474).

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Main outcome measures: Rate of detection of LGA (estimated fetal weight on ultrasound scan above the 90th centile after 34^{+0} weeks of gestation, defined by either population or customised growth charts), maternal and perinatal outcomes (e.g. mode of birth, postpartum haemorrhage, severe perineal tears, birthweight and gestational age, neonatal unit admission, perinatal mortality, and neonatal morbidity and mortality).

Results: A total of 506 LGA babies were exposed to GAP and 618 babies received standard care. There were no significant differences in the rate of LGA detection (GAP 38.0% vs standard care 48.0%; adjusted effect size −4.9%; 95% CI −20.5, 10.7; $p = 0.54$), nor in any of the maternal or perinatal outcomes.

Conclusions: The use of GAP did not change the rate of antenatal ultrasound detection of LGA when compared with standard care.

KEYWORDS
antenatal screening, big baby, Growth Assessment Protocol, large for gestational age

1 | INTRODUCTION

Babies that are large for gestational age (LGA) are those with a birthweight above the 90th centile for gestational age. Mothers of LGA or macrosomic (birthweight greater than 4.0–4.5 kg) babies are at higher risk of intrapartum complications (prolonged labour, assisted vaginal birth, emergency caesarean section, shoulder dystocia, perineal trauma and haemorrhage), and possibly stillbirth. The babies have greater risk of neonatal complications (low Apgar score, neonatal unit admission, neonatal trauma, transient tachypnoea, hyperbilirubinaemia or hypoglycaemia).[1–6]

Unlike the universal screening programmes for fetuses that are small for gestational age (SGA), guidelines on antenatal care do not recommend routine screening for LGA.[7,8] Conversely, serial ultrasound fetal growth assessment is recommended for women with diabetes or with a body mass index (BMI) of ≥35.0 kg/m^2 in pregnancy,[9–11] both associated with LGA. Antenatal ultrasound diagnosis of LGA/macrosomia has only moderate sensitivity (53.2%), although it has good specificity (93.9%) for LGA/macrosomia at birth.[12] However, the sensitivity decreases with increasing fetal weight.[13,14] A cost-effectiveness analysis of universal ultrasound screening for fetal macrosomia identified insufficient health benefits to justify the practice.[15]

Screening programmes intended to monitor for SGA fetuses can lead to the incidental identification of LGA, causing potential maternal anxiety, without clear strategies for further management.[8,16] The Growth Assessment Protocol (GAP) is a complex antenatal intervention that aims to improve the antenatal detection of SGA and reduce stillbirth, through staff training, risk stratification and surveillance protocols, assessment of fetal growth using customised 'Gestation Related Optimal Weight' (GROW) charts, audit and missed-case analyses. Its use is widespread in the UK, Australia and New Zealand.[17,18] GAP implementation is not intended to screen for LGA, but the guidelines recommend that an accelerative fundal height trajectory should initiate referral for a fetal growth ultrasound assessment. Qualitative evaluation of the acceptability of GAP during the DESiGN trial (a randomised control trial that compared the effectiveness of GAP on the antenatal detection of SGA to that achieved with standard care) identified concerns amongst healthcare staff that GAP was inadvertently leading to the identification of LGA babies, causing anxiety amongst women about giving birth to a 'big baby' and uncertainty amongst clinicians about which management strategies to offer.[19]

The objective of this pre-specified secondary analysis of the DESiGN trial was to determine whether GAP changes the rate of antenatal detection of LGA babies born at ≥36^{+0} weeks of gestation or affects maternal and perinatal outcomes of LGA fetuses, compared with sites continuing to administer standard care.

2 | METHODS

2.1 | Study design

This was a pre-specified secondary analysis of the DESiGN trial, a randomised 1:1 cluster control trial that compared the rate of antenatal detection of SGA in cluster sites implementing GAP, with sites continuing to provide standard care. The full study protocol and primary trial results (including CONSORT diagram) have been published in full.[20,21] This secondary analysis was conducted to determine whether GAP had an effect on the detection of LGA and subsequent maternal or perinatal outcomes of LGA babies. It is important to note that, as a secondary analysis, the trial was not statistically powered to find a change in the detection rate for LGA and the ability for us to detect a difference in the detection of LGA was further reduced by the loss of one cluster site from the analysis of the primary outcome.

This UK trial was conducted between 5 November 2016 and 28 February 2019. Thirteen maternity units (clusters)

were recruited and randomly allocated to either the implementation of GAP or to continued standard care (where it was stipulated that they should not implement GAP or assess fetal growth using customised centile charts). The sample size was determined by the trial primary outcome (effect of GAP on the detection of SGA). Two clusters did not contact the GAP provider to commence implementation and so were excluded from this analysis (modified intention-to-treat analysis).

Singleton, non-anomalous babies born after 24^{+0} weeks of gestation during the trial outcome period (variable period of 4–6 months, from 1 July 2018 and 28 February 2019) and during the pre-randomisation period (variable 12-month continuous period between 5 November 2015 and 4 July 2017) were included. Periods varied according to the date of cluster randomisation into the study.

This study has been reported according to the recommendations of the CONSORT checklist with cluster extension for reporting the results of randomised control trials.[22] The completed checklist is included in Appendix S1.

2.2 | Outcomes

The primary outcome of this study is the rate of antenatal ultrasound detection of LGA at $\geq 34^{+0}$ weeks of gestation in infants who were confirmed to be LGA by both customised (GROW) and population (UK 1990) centile charts (LGA_{both}) when born at $\geq 36^{+0}$ weeks gestation.[23,24] Antenatal LGA was defined as an estimated fetal weight (EFW) above the 90th centile on population fetal weight charts for births in both trial arms during the pre-randomisation phase and births in the standard care arm during the outcome phase. For babies born in GAP-implementing clusters during the outcome period, we defined LGA as an EFW above the 90th centile on customised GROW fetal weight charts (because these were employed as part of the intervention).

Secondary outcomes of this study included a variation of the primary outcome with LGA at birth defined by customised charts (LGA_{cust}) and separately by population charts (LGA_{pop}), and screening outcomes (e.g. false-positive rate) for each definition of LGA (LGA_{both}, LGA_{cust}, $LGAP_{pop}$). We also recorded ultrasound use in women giving birth to an LGA_{both} baby at $\geq 36^{+0}$ weeks of gestation: the proportion of women receiving any ultrasound; the number of scans; the proportion of women receiving an ultrasound scan at $\geq 34^{+0}$ weeks of gestation (with or without EFW); and the number of scans received at $\geq 34^{+0}$ weeks of gestation. Finally, we assessed maternal (induction of labour, mode of birth, postpartum haemorrhage, severe perineal trauma (third or fourth-degree tear), episiotomy and epidural use) and perinatal outcomes known to be associated with LGA (mean gestational age at birth, birth $<39^{+0}$ weeks of gestation, mean birthweight, Apgar score of <7 at 5 minutes, umbilical arterial cord pH of <7.10, admission to a neonatal unit, hypoxic ischaemic encephalopathy, neonatal hypoglycaemia and nasogastric tube feeding).

2.3 | Management of missing data

The proportion of pregnancies in which the baby was born LGA and for which we were missing data on maternal or perinatal characteristics was assessed (Table S2). The rate of missing data for all women included within the trial and the management of missing data in this trial has previously been described.[25] For ease of reference, missing values were multiply imputed through chained equations (MICE), with ten imputations under the missing-at-random assumption. Predictors included pregnancy characteristics and the trial primary outcome. Variables were imputed within cluster, wherever possible.

For ultrasound use, if there was no record of a scan, it was assumed that the woman had not received an ultrasound at that cluster. For two sites in the intervention arm, data were missing on EFW for some groups of women. There were no data on EFW for LGA babies at one site, which was excluded from measures related to screening outcomes. At another site, data were missing on EFW of all babies during the pre-randomisation phase only; these data were only required for adjusting results by the baseline rate. At this site, we imputed the cluster rate of antenatal detection of LGA during the pre-randomisation phase by predicting the mean number of ultrasound scans received after 34 weeks of gestation from the rates for all other clusters during the same time period.

All results are primarily presented using multiply imputed missing data, where appropriate. A sensitivity analysis using available case data was conducted and results are reported in the Tables S3-S7.

2.4 | Statistical analyses

Maternal and neonatal characteristics were compared between trial arms and phases for births in which the baby was born LGA_{both} using frequency and percentage, mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate (dependent on data distribution). The number and proportion of babies who were LGA_{both}, LGA_{cust} and LGA_{pop} at birth were calculated and stratified by gestational age for birth categories. Further analyses are only conducted using data from pregnancies in which the baby was born LGA at $\geq 36^{+0}$ weeks of gestation.

The numbers and percentages of LGA_{both}, LGA_{pop} and LGA_{cust} babies who were antenatally detected by ultrasound at $\geq 34^{+0}$ weeks of gestation in each arm of the trial were calculated. In all cases, the numerator was the number of babies in the denominator for whom the EFW from the last recorded fetal growth ultrasound scan was greater than that for the 90th centile (using Hadlock fetal charts for the population reference definition and GROW charts for the customised standard definition).[23,26] Screening outcomes, measures of ultrasound use, and maternal and perinatal outcomes are also presented by trial arm, using summary statistics and unadjusted differences. The differences between trial arms for each outcome were adjusted

using a two-stage cluster summary approach,[27] in which cluster summary values for the pre-randomisation and outcome phases were first adjusted by the ethnicity, age and parity of the individual participants. In the second phase, a linear regression analysis (analysis of covariance, ANCOVA) was used in which the adjusted cluster summary values for outcomes in the outcome period were compared between the trial arms, adjusting for a stratification factor (related to cluster size and time of randomisation), and the baseline (pre-randomisation) adjusted cluster summary value for that outcome. For each outcome we present an adjusted difference between the trial arms, reported with a 95% confidence interval and a *p*-value based on the Student's *t*-distribution with degrees of freedom equal to the number of clusters minus two. No subgroup analyses were planned.

2.5 | Core outcome sets

We were unable to identify a core outcome set specific to research assessing outcomes for LGA or macrosomic babies.

2.6 | Patient involvement

A lay representative from Guy's and St Thomas' Charity was involved as a co-investigator throughout the DESiGN trial. His participation was invited to gain patient/public perspectives on research need, planned study design (including the acceptability of data collection methods) and impact from the interpretation of the results. He has reviewed and commented on protocol development, ethics applications and interpretation of the results, which were all received positively without significant recommendations for change.

3 | RESULTS

Of the 80 856 women and babies included across both arms of the pre-randomisation and outcome comparison phases of the trial, 5.36% were LGA_{both}, 1.4% were LGA_{pop} but not LGA_{cust} and 3.0% were LGA_{cust} but not LGA_{pop}. The majority of LGA babies (95.4%) were born at $\geq 36^{+0}$ weeks of gestation. The number and proportion of babies who were LGA by each definition, including when stratified by gestational age, are available by trial arm in Table S1 (imputed data).

The characteristics of the women and their LGA_{both} babies born during the outcome comparison trial phase are summarised in Table 1 (results presented use imputed data where characteristics were imputed and available case data [non missing data] where characteristics were not imputed). Compared with women giving birth to LGA_{both} babies at cluster sites in the trial arm for standard care, women giving birth to LGA_{both} babies at clusters in the intervention arm were of a similar age (GAP 32.6 years vs standard care 33.0 years), a higher proportion were nulliparous (36.8% vs 29.9%) or Asian (15.9% vs 8.9%) and fewer were white (62.6% vs 66.6%) or black (13.2% vs 16.5%), a lower proportion lived in the least deprived areas (8.8% vs 22.3%); they had similar BMIs (26.8 kg/m^2 vs 26.6 kg/m^2). Rates of smoking were also similar between the trial arms.

The percentage of women who had received at least one scan during pregnancy at the cluster site in which they gave birth to an LGA_{both} baby was similar in trial arms (GAP 94.8% vs standard care 94.5%; $p = 0.23$); however, there was strong evidence to suggest that babies exposed to GAP had a lower total number of scans than those exposed to standard care (3.8 vs 4.7; adjusted effect size −0.9; 95% CI −1.3, −0.5; $p < 0.01$). There was no statistically significant difference in the proportion of women who received an ultrasound scan after 34^{+0} weeks of gestation (62.2% vs 73.0%; adjusted effect size −14.2%; 95% CI −34.7, 6.4; $p = 0.14$). The use of ultrasound scans for women giving birth to an LGA_{both} baby in both trial arms and phases is detailed in Table S2.

There was no significant difference in the rate of detection of LGA_{both} after 34 weeks of gestation for babies born at $\geq 36^{+0}$ weeks of gestation (GAP 38.0% vs standard care 48.0%; adjusted effect size −4.9%; 95% CI −20.5, 10.7; $p = 0.54$). The intra-cluster correlation coefficient for the rate of detection of LGA_{both} was 0.028. There were also no differences in the false-positive rate, the rate of detection using other definitions of LGA or any of the other screening test statistics studied. The screening outcomes for mothers and their LGA babies are available in Table 2 (imputed data).

There were no differences in secondary outcomes for mothers giving birth to LGA_{both} babies at $\geq 36^{+0}$ weeks of gestation between the standard care and intervention arms of the DESiGN trial (Table 3). There were also no differences between trial arms for any of the neonatal outcomes (Table 4). There were too few events in either arm or in both arms to estimate an adjusted effect size for stillbirth and perinatal death; there were no differences in the unadjusted estimates.

3.1 | Sensitivity analyses

The results of a sensitivity analysis including only available case data are included in Tables S3–S7. There remained no significant difference in the rate of detection of LGA between trial arms when LGA was defined by any definition. There were no differences in the findings on use of ultrasound when examined for LGA babies as defined by available case data only (ultrasound data was not otherwise imputed). For the available case analysis – there was only evidence of a lower rate of major obstetric haemorrhage (postpartum bleeding of >1500 mL; adjusted effect size −2.40%, 95% CI −4.77, −0.03; $p = 0.048$) in the intervention arm, which should be interpreted with caution given the number of statistical tests performed.

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TABLE 1 Clinical and sociodemographic characteristics of pregnancies in which the baby was born LGA during the outcome comparison trial phase, presented by trial arm

	Standard care	GAP
	LGA_{both} ($n \approx 618$, 6 clusters)	LGA_{both} ($n \approx 506$, 5 clusters)
Imputed data		
Age at estimated conception, median (IQR), years	33.0 (29.3–36.1)	32.6 (28.8–36.5)
Ethnicity, %		
White	66.6	62.6
Black	16.5	13.2
Asian	9.0	15.9
Mixed	1.4	0.9
Other	6.5	7.5
Index of multiple deprivation quintiles, %		
1 (least deprived)	22.3	8.8
2	13.9	12.2
3	14.6	24.6
4	26.0	31.7
5 (most deprived)	23.2	22.7
Body mass index, median (IQR), kg/m^2	26.6 (23.4–31.5)	26.8 (23.4–31.6)
Parity, %		
Nulliparous	29.9	36.8
1	44.2	39.2
2	14.4	14.6
3	6.9	5.3
4+	4.6	4.0
Non-imputed data		
Smoking in pregnancy, *n* (%)[a]	20 (3.2)	13 (2.9)
Missing smoking, *n* (%)	15 (2.4)	43 (8.6)
Pre-existing comorbidities, *n* (%)		
Diabetes[a]	25 (6.1)	32 (7.7)
Missing diabetes	225 (35.6)	82 (16.5)
Hypertension[a]	8 (1.9)	9 (2.1)
Missing hypertension	219 (34.6)	62 (12.5)
Antenatal complications, *n* (%)		
Gestational diabetes (GDM)[a]	57 (11.5)	55 (13.6)
Missing GDM	137 (21.6)	92 (18.5)
Gestational hypertension[a]	12 (3.2)	25 (14.5)
Missing gestational hypertension	256 (40.4)	325 (65.4)
Infant sex		
Infant sex, male, *n* (%)[a]	370 (58.5)	271 (54.5)
Missing infant sex	0 (0.00)	0 (0.00)

[a]Mothers and babies with missing data have been excluded from the denominator.

4 | DISCUSSION

4.1 | Main findings

In this secondary analysis of the DESiGN trial, there were no significant differences in the rate of detection of LGA, when LGA was defined using either population, customised or both charts (primary rate of detection definition: 38.0% with GAP and 48.0% with standard care; mean difference −4.9%; 95% CI −20.5, 10.6; $p = 0.54$), nor in maternal or neonatal outcomes. Although the effect size of the primary outcome suggests a lower rate of detection using

TABLE 2 Rate of detection of LGA by different definitions, presented by trial arm and phase (imputed data)

	Pre-randomisation phase		Comparison phase				
	Standard care (6 clusters)	GAP (4 clusters)	Standard care (6 clusters)	GAP (4 clusters)	Intervention effect size Unadjusted (95% CI)	Intervention effect size Adjusted (95% CI)	*p*
Primary outcome							
LGA_{both} at birth, %	5.7	5.4	4.7	4.8			
Antenatal detection, %	24.1	38.0	48.0	38.1	−6.2 (−21.1, 8.7)	−4.9 (−20.5, 10.6)	0.53
False-positive rate[a], %	3.3	2.6	7.1	4.8	−2.8 (−6.1, 0.6)	−1.9 (−4.4, 0.6)	0.13
Secondary outcomes							
All LGA_{cust} at birth, %	8.7	8.5	7.5	7.6			
Antenatal detection, %	19.0	29.8	38.2	36.1	0.8 (−13.6, 15.2)	0.9 (−13.3, 15.1)	0.90
False-positive rate[a], %	3.1	2.4	6.7	3.9	−3.2 (−6.4, 0.1)	−2.0 (−4.4, 0.5)	0.12
All LGA_{pop} at birth, %	7.0	6.7	6.3	6.2			
Antenatal detection, %	23.2	36.9	45.2	33.1	−10.3 (−21.5, 0.9)	−7.4 (−19.8, 5.1)	0.25
False-positive rate[a], %	3.1	2.4	6.6	4.7	−2.3 (−5.5, 0.8)	−1.5 (−3.7, 0.7)	0.18

[a]One site did not contribute data on the detection of LGA during the pre-randomisation phase. A pre-randomisation estimate was imputed at the cluster level for the rate of LGA detection (any definition) at this site to enable the calculation of the adjusted effect size; the cluster was excluded from the results for other screening outcomes.

TABLE 3 Secondary outcomes for mothers who gave birth to LGA_{both} babies at $\geq 36^{+0}$ weeks of gestation, presented by trial arm and phase (imputed data)

	Pre-randomisation phase		Comparison phase				
	Standard care $n \approx 1607$[a] 6 clusters	GAP $n \approx 1358$[a] 5 clusters	Standard care $n \approx 627$[a] 6 clusters	GAP $n \approx 513$[a] 5 clusters	Intervention effect size Unadjusted (95% CI)	Intervention effect size Adjusted (95% CI)	*p*
Induction of labour, %	24.4	29.9	24.8	31.1	8.1 (−3.0, 19.2)	1.6 (−2.4, 5.6)	0.42
Mode of birth, %							
Spontaneous vaginal delivery	45.4	49.1	43.1	42.7	0.9 (−9.5, 11.4)	−2.0 (−5.1, 1.1)	0.21
Instrumental delivery	9.6	12.0	9.7	10.3	1.6 (−4.1, 7.3)	−0.1 (−3.5, 3.3)	0.95
Elective caesarean section	25.5	23.7	29.8	28.9	−3.3 (−16.2, 9.6)	−1.2 (−6.8, 4.3)	0.67
Emergency caesarean section	19.5	15.0	17.4	18.2	0.7 (−3.3, 4.7)	−0.1 (−2.7, 2.5)	0.92
Estimated blood loss, mean (SD), ml	625.7 (482.1)	638.0 (481.7)	652.6 (550.6)	642.6 (454.1)	−31.9 (−117.1, 53.4)	−12.7 (−64.7, 39.3)	0.63
Post-partum haemorrhage (>1500 ml), %	5.5	4.4	6.1	4.12	−2.5 (−5.5, 0.4)	−1.5 (−3.8, 0.8)	0.21
3rd/4th-degree tears[b], %	2.2	3.0	1.4	2.2	1.4 (−1.1, 3.9)	1.0 (−1.0, 2.9)	0.33
Epidural[b], %	31.6	29.1	31.6	29.1	−5.3 (−23.5, 12.9)	2.4 (−7.8, 12.5)	0.65
Episiotomy[b], %	12.3	18.5	13.4	14.7	14.5 (−7.8, 36.8)	−4.4 (−9.2, 0.4)	0.07

[a]Estimated for imputed data set.

[b]These outcomes were not imputed.

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TABLE 4 Secondary outcomes for LGA_{both} babies born at $\geq 36^{+0}$ weeks of gestation, presented by trial arm and phase (imputed data)

	Pre-randomisation phase		Comparison phase				
	Standard care $n \approx 1607$[a] 6 clusters	GAP $n \approx 1358$[a] 5 clusters	Standard care $n \approx 627$[a] 6 clusters	GAP $n \approx 513$[a] 5 clusters	Intervention effect size Unadjusted (95% CI)	Intervention effect size Adjusted (95% CI)	*p*
Gestational age at birth, mean (SD), weeks	39.3 (1.3)	39.2 (1.34)	39.2 (1.25)	39.3 (1.28)	0.1 (−0.1, 0.2)	0.1 (−0.1, 0.2)	0.30
Birth before 39^{+0} weeks of gestation, %	36.6	38.9	39.5	37.5	−2.1 (−9.3, 5.1)	−2.8 (−8.2, 2.7)	0.32
Birthweight, grams, mean (SD)	4208.0 (352.6)	4179.4 (372.3)	4184.3 (338.9)	4196.2 (333.1)	18.5 (−19.5, 56.6)	24.6 (−2.4, 51.6)	0.07
Apgar score <7 at 5 min[b], %	1.8	1.7	2.4	1.3	−1.0 (−2.4, 0.4)	0.4 (−1.8, 0.9)	0.53
Arterial cord pH <7.1[b], %	2.8	3.1	2.8	3.4	0.2 (−1.9, 2.4)	0.2 (−1.2, 1.5)	0.81
Neonatal unit admission[b], %	16.1	10.8	19.9	9.3	−10.0 (−27.9, 7.9)	−1.1 (−4.7, 2.5)	0.54
Hypoxic-ischaemic encephalopathy[b], %	0.1	0.2	0.3	0.6	0.2 (−0.4, 0.8)	0.5 (−0.1, 1.1)	0.12
Hypoglycaemia[b], %	2.3	2.9	2.9	2.0	−0.4 (−2.6, 1.7)	0.4 (−1.9, 2.6)	0.75
Nasogastric tube feeding[b], %	1.2	2.8	1.6	2.8	0.9 (−1.1, 2.9)	0.4 (−1.3, 2.1)	0.64
Stillbirth[b], %	0.0	0.2	0.2	0.0	−0.2 (−0.5, 0.2)	–[c]	–[c]
Neonatal death[b], %	0.0	0.0	0.0	0.0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00
Perinatal mortality[b], %	0.0	0.2	0.2	0.0	−0.2 (−0.5, 0.2)	–[c]	–[c]

[a]Estimated for imputed data set.

[b]These outcomes were not imputed.

[c]Cannot be calculated because there were too few events.

GAP, particularly as women exposed to GAP had one fewer growth scan per pregnancy, the wide 95% CIs cross zero and the difference is small (a more clinically important effect is possible, given that up to a 20% difference was included within the 95% CIs).

Sensitivity analysis using available case data identified a lower rate of major postpartum haemorrhage for women exposed to GAP and a trend towards lower rates of assisted vaginal birth and episiotomy; however, these findings were not repeated with the primary, imputed analysis. Although it is possible to speculate that if LGA detection was lower in GAP-implementing clusters then clinicians were less likely to perform instrumental birth, and this in turn might have resulted in lower rates of episiotomy and haemorrhage, it is important to note that these findings were not repeated with the primary, imputed analysis.

4.2 | Strengths and limitations

This is a secondary analysis of a pragmatic randomised controlled trial (RCT) that explored the effect of GAP under real-world conditions and therefore captured, as closely as possible, the real effects of GAP. This is its primary strength. Furthermore, standard care and GAP both diagnose LGA using different references, and thereby LGA_{pop} is not wholly relevant to maternity units implementing GAP, or vice versa for LGA_{cust}. By choosing LGA_{both} as our primary definition, we can directly compare the detection rates of two chart types.

The main limitation is that the DESiGN trial was statistically powered to find a change in the detection rate for SGA, but not for LGA. Our statistical power to detect a difference in LGA detection was further reduced by the loss of one cluster site from the analysis, evidenced by wide confidence intervals.

Furthermore, data collection was prioritised towards enabling the primary analysis of the trial (detection of SGA). In addition to exclusion of data on LGA screening outcome from one site, the rate of detection was also missing during the pre-randomisation phase for another site and therefore imputed. Data on shoulder dystocia and some of its consequences, e.g. brachial plexus injury, were not collected. Nevertheless, we did not find a difference in other

consequences of shoulder dystocia: neonatal unit admission, hypoxic ischaemic encephalopathy or low Apgar scores. Data quality and completeness for maternal diabetes (commonly associated with an LGA fetus) was poor.

We expect that the study findings are generalisable to maternity units with a similar fidelity of GAP implementation and resource availability.[19]

4.3 | Interpretation (in light of other evidence)

During the process evaluation of the DESiGN trial, members of staff implementing GAP expressed concerns that it was causing an increase in the detection of LGA babies without clear local guidance on what care to offer women following an LGA diagnosis.[19] UK guidance on this topic was not available at the time of the trial, although brief guidance has subsequently been published by the National Institute for Health and Care Excellence (NICE), in 2019.[28] Contrary to staff perceptions, we found no difference in the rate of LGA detection, including the test-positive rate. Furthermore, the rate of detection noted in this study is lower than the meta-analysis reported sensitivity of ultrasound screening for LGA/macrosomia in mixed/low-risk populations, possibly because our trial sites only offered growth scans selectively to women with risk factors or because of differences in definitions.[29] An earlier study reported a similar performance of Hadlock and GROW charts in the prediction of LGA at birth, but only amongst women who were obese.[30] It is possible that the perceived increase in LGA detection was driven by high fundal height measurements that were not referred for scans, as the GAP protocol recommends that a first measurement above the 90th centile is not an indication for a growth scan, unless the growth trajectory is accelerative.[31]

Women giving birth to LGA babies in the standard care arm of the DESiGN trial had more ultrasound scans during pregnancy, with the difference occurring primarily in scans after 34 weeks of gestation. Although GAP does not recommend that a fundal height plot above the 90th centile trigger a fetal growth scan,[31] half of the guidelines received from maternity clusters applying standard care did recommend this. Nevertheless, this difference in the number of ultrasound scans did not translate into a statistically significant difference in the rate of antenatal detection of LGA, which may be linked to the statistical power or to the established inaccuracy of estimating fetal weight, which is magnified for babies with the highest weights (generally underestimated), causing missed diagnoses.[12,13,32,33]

There is little consensus with respect to the optimal management of pregnancies with a suspected LGA fetus. A Cochrane review reported that induction of labour at or near term resulted in lower rates of shoulder dystocia and fetal fractures, based on four trials. For the mothers, the review found no difference in modes of birth but higher rates of severe perineal trauma (reported only from one study).[34] Given that this systematic review was dominated by a single RCT,[35] and still presents uncertainty regarding some perinatal and maternal outcomes, further research is needed. Although the DESiGN trial evidenced that staff perceive an increased anxiety amongst women who are told that they have a big baby, research focused on women's actual experience would be valuable. Furthermore, the outcomes studied in trials included within the Cochrane review were heterogenous. The development of a core outcome set would improve the ability to compare and combine study findings in this area.

The 'Big Baby Trial' is currently underway (expected completion in 2023),[36] to determine whether induction of labour at 38 weeks of gestation for babies suspected to be LGA, compared with expectant management, reduces the incidence of shoulder dystocia. If this also finds that intervention is indicated, it will then be necessary to explore whether selective or universal screening for LGA also contributes to an improvement of outcomes.

4.4 | Conclusion

The GAP was not found to increase the ultrasound detection of LGA after 34^{+0} weeks of gestation amongst LGA or all babies born at $\geq 36^{+0}$ weeks of gestation, when compared with standard care in the DESiGN trial. Women giving birth to LGA babies and receiving care in GAP-implementing clusters received fewer fetal growth scans than those receiving care in clusters continuing with standard care. This difference is likely to have been caused by guidelines applicable to the standard care arm that had varied recommendations on referral for suspected LGA. Further research is needed from RCTs to inform clinicians on the safest and most cost-effective methods to manage pregnancies with suspected LGA, followed by further statistically powered research on the clinical usefulness and efficacy of routine screening for LGA.

AUTHOR CONTRIBUTIONS

DP is the Chief Investigator of the DESiGN trial. SR, MCV, AC and DP designed this study. SR obtained the data locally and oversaw the data management procedures, conducted with the data management team. SR conducted the analysis. SR, MCV and DP reviewed and interpreted the results. SR drafted the article. All authors have reviewed the draft article, provided feedback, and read and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

NM reports personal fees from Takeda, personal fees from RSM Consulting and personal fees from Novartis, outside this work. BT is the Clinical Director and JS is a Programme Lead of the Tommy's National Centre for Maternity Improvement, based at the Royal College of Obstetrics and Gynaecology; the objective of the centre is to translate the latest evidence into clinical practice in the UK. JS is also Head of Maternity and Midwifery Research at NHS England. Completed disclosure of interests form available to view online as supporting information. LP is Deputy Clinical Director, Maternity Investigation Programme, Healthcare Safety Investigation Branch. JS is also Head of Maternity and Midwifery Research at NHS England.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly because consent was not obtained from the women; permission for sharing data was not sought as part of the ethics approval. Data are only available following approval from the Research Ethics Committee and Confidentiality Advisory Group. Enquiries and requests should be made to the DESiGN trial team and sponsors through the Department of Women and Children's Health at King's College London (solcs_research@kcl.ac.uk).

ETHICS APPROVAL

Ethics approval for the DESiGN trial was obtained through the Health Research Authority (HRA) Integrated Research Applications System (IRAS) from the London Bloomsbury Research Ethics Committee (ref. 15/LO/1632) and the Confidentiality Advisory Group (ref. 15/CAG/0195). King's College London is the sponsor for this trial.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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