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Title Page

Title

The impact of a universal late third-trimester scan for fetal growth restriction on perinatal outcomes in term singleton births: a prospective cohort study

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Running title:

Universal late pregnancy scan for adverse perinatal outcomes

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Abstract

Objective

To investigate perinatal mortality, morbidity and obstetric intervention following the introduction of a universal late third-trimester ultrasound scan for growth restriction.

Design

Prospective cohort study

Setting

Oxfordshire (OUH), UK

Population

Women with a non-anomalous singleton pregnancy undergoing pregnancy care and term delivery at OUH with an estimated date of birth between 01/Jan/2014 and 30/Sept/2019.

Methods

Universal ultrasound for fetal growth restriction between 35^{+0} and 36^{+6} weeks was introduced in 2016. The outcomes of the next 18631 eligible term pregnancies were compared, adjusting for covariates and time, with the previous 18636 who had clinically-indicated ultrasounds only. 'Screen positives' for growth restriction were managed according to a pre-determined protocol which included non-intervention for some SGA babies.

Main Outcome Measures

Extended perinatal mortality, a composite of mortality or encephalopathy Grade II-III, and expedited birth. Other outcomes included composite adverse outcomes used elsewhere, detection of low birthweight and birth from 37^{+0} to 38^{+6} weeks.

Results

Extended perinatal deaths decreased 27% and severe morbidity decreased 33% but neither change was statistically significant (aOR 0.53; 00.18-1.56 and aOR 0.71; 0.31-1.63). Expedited births changed from 35.2% to 37.7% (aOR: 0.99 (0.92 – 1.06). Birthweight ($<10^{th}$ centile) detection using fetal biometry alone was 31.4% and rose to 40.5% if all abnormal scan parameters were used.

Conclusion

Improvements in mortality and severe morbidity subsequent to introducing a universal ultrasound for growth restriction are encouraging but remain unclear. Little change in intervention is possible. The antenatal detection of low birthweight remains poor but improves where markers of growth restriction are used.

Keywords

Universal ultrasound, late pregnancy, 36-week, fetal growth restriction, FGR, perinatal morbidity and perinatal mortality.

Tweetable abstract

Introducing a universal late third trimester ultrasound scan, with management by protocol, might reduce some adverse pregnancy outcomes with little change in pregnancy interventions.

What are the novel findings of this work?

The introduction of a universal ultrasound-based screening test for FGR is followed by non significant reductions in extended perinatal mortality or severe morbidity. Detection of low birthweight increases best where criteria for growth restriction are used in addition to estimated weight. Despite increased workload, pregnancy intervention was altered little by using a management protocol.

What are the clinical implications of this work?

Introducing a universal late pregnancy ultrasound is feasible but mortality will probably only be significantly reduced by incorporating other risk factors in a prediction model to better target intervention.

Introduction

Perinatal mortality and severe morbidity remain major problems in high-income settings.[1,2] Preventive strategies are limited: the principal strategy is expedited birth of at-risk fetuses. Attention focuses on identifying babies born small for gestational age (SGA) because they are at a disproportionately increased risk of stillbirth[1,3] and the risk is reduced if birthweight (<10th-centile) is identified antenatally.[4,5]

The use of third-trimester ultrasound is increasing, largely based on a guideline, risk factor-based strategy.[6] Given the limited predictive value of these risk factors and the potential for human error[2] and concerns regarding equity, 'universal' ultrasound has been explored.[7,8] Evidence suggests this increases the detection rate of birthweight (<10th-centile),[7,8] but does not improve perinatal outcomes[8,9], not least because many SGA babies are not growth restricted[10,11] and birthweight (<10th-centile) comprise less than a quarter of stillbirths.[3] Nevertheless, impaired placental function may be present in about half of stillbirths,[12] and the concept of fetal growth restriction (FGR) has developed[13]. The most promising ultrasound-based additional predictors are growth velocity[7] and Doppler parameters of the placental or fetal circulations[14,15]. The potential exists to incorporate these in a late pregnancy screening test.

A screening test requires an effective intervention. In well SGA fetuses, intervention could cause harm: early-term birth is associated with increased infant mortality,[16] and impaired cognitive and neurological development.[17–20] The management of screen positives has been unclear in screening studies using ultrasound.[8,21] Harm could also result when a fetus is incorrectly classified as SGA, principally because of ultrasound inaccuracy[23.] Nevertheless, evidence-based algorithms may reduce intervention, allowing expedited birth to be targeted to those at most risk.[22,23]

In 2016 a universal 36-week ultrasound scan was introduced for all pregnant women at the Oxford University Hospitals NHS Foundation Trust (OUH): the Oxford Growth Restriction Identification Programme (OxGRIP). This study aims to investigate the impact of the OxGRIP initiative in the

population of women who gave birth in Oxfordshire in the study period on perinatal morbidity and mortality.

Methods

Study design and participants

This is cohort study of women who had pregnancy care and gave birth at the OUH with a singleton pregnancy, an estimated date of delivery (EDD) between 01/Jan/2014 and 30/Sept/2019, and booked for care before 20 weeks. Exclusion criteria were: non-singleton pregnancy; known major fetal anomaly; women referred only for tertiary care; and birth $<37^{+0}$ weeks' gestation. The cohort was divided into two time periods, before and after the introduction of the OxGRIP initiative.

Setting

The OUH comprises one large obstetric unit at the John Radcliffe Hospital, Oxford; four midwifery-led units (MLUs); and one unit which was a consultant-led unit until 30/Sept/2016 and an MLU thereafter. There are approximately 7500 births per annum. The John Radcliffe Hospital also has a tertiary fetal and maternal medicine service, a level-3 neonatal intensive care unit (NICU) and paediatric surgical facilities.

All women (excepting IVF pregnancies) were dated by crown rump length (CRL) between 11^{+0} and 13^{+6} weeks or, if booking after this, by measurement of head circumference (HC); a scan between 19^{+0} and 20^{+6} weeks was always performed for detection of structural abnormalities. Throughout the study period, later ultrasound examinations, +/- intervention, were conducted if fetal growth was suboptimal, in a consultant-led 'growth' clinic. At this, all fetal measurements were repeated, with assessment of umbilical artery (UmbA) pulsatility index (PI), middle cerebral artery (MCA) PI, uterine artery PI, cerebroplacental ratio (CPR) and calculation of low abdominal circumference (AC) growth velocity, defined as a >40-centile reduction from the 20-week scan. Expectant management or expedited birth was offered (Fig S1) according to a modification of a published protocol[22].

Exposure

Before OxGRIP implementation, women with an EDD before 01/Oct/2016 had ultrasound scans at any gestation as considered clinically indicated, on the basis of risk factors or new pregnancy complications[24]. The EFW and UmbA-PI were recorded. Suspected SGA fetuses with EFW<10thcentile or umbA-PI> 95th-centile were referred to the growth clinic.

Following OxGRIP implementation, all women with an EDD from 01/Oct/2016 were offered a universal ultrasound between 35^{+0} and 36^{+6} weeks. The EFW, UmbA-PI, MCA-PI, CPR and AC growth velocity were recorded. Women were considered 'screen positive' and referred for secondary assessment not only when EFW <10th-centile, or when UmbA PI >95th-centile, but also if the CPR<1.1, or if there was a >40-centile point AC growth deceleration compared to the 20-week scan (Fig S1). In addition, all pregnancies within the implementation time had uterine artery Doppler performed at the time of the anomaly scan: this was only used to determine routine scans prior to 35 weeks.

Outcomes

Outcomes for the period before and after OxGRIP implementation were compared. *A priori* primary outcome measures were: 1) extended perinatal mortality - stillbirths and neonatal deaths up to 28 days per 1000 total births; 2) composite adverse perinatal outcome-1 (CAPO-1) defined as extended perinatal mortality or Sarnat's[25] encephalopathy grade II or III : a surrogate for 'mortality or severe morbidity'; and 3) expedited birth, defined as induction of labour or pre-labour caesarean section. Several *a priori* secondary outcomes of perinatal mortality and morbidity were used (defined in the footnotes of tables). Breech presentation was not presented as this has been previously reported.[26]

Equipment and staff

All ultrasound examinations were performed by accredited sonographers or clinical fellows using GE Healthcare E6,E8, E10 or Philips EPIQ 7 machines. Measurements were transferred electronically using the standard Digital Imaging and Communications in Medicine (DICOM) format; and stored in a digital database using the archiving software Viewpoint version™ 5.6.25.281, (GE Healthcare). All

sonographers were locally trained in the new guidelines and referral pathways. Random image analysis and measurement distributions were audited for quality control.[27]

Public and patient involvement (PPI)

A PPI focus group consisting of 5 user representatives was consulted in April 2016 and questionnaires were handed to the first 250 women undergoing a routine third-trimester scan. Of these, unit data shows that all but one (99.6%) welcomed the scan, although 24 (9.6%) felt more anxious after it.

Data sources and definitions

Routinely collected maternal, fetal and neonatal follow-up data were sourced from electronic patient records (maternal: Cerner Millennium®, London, UK; neonatal: Badgernet®, Clevermed, Edinburgh, UK) and the ultrasound database (Viewpoint™ version 5.6.25.281, GE Healthcare). Using unique study identifiers for each pregnancy, data were merged to create a dataset containing mother-baby pairs. Source documents for all extended perinatal deaths and severe morbidity were also manually reviewed.

De-identified demographic data and clinical variables were extracted. Body mass index was classified as per a modification of World Health Organization criteria with all obesity classes grouped together .[28] Ethnicity was categorized as white; black or African descent; Asian or Asian descent; or mixed. Socioeconomic status was based on the index of multiple deprivation (IMD) quintile using residential postcode.[29] Maternal hyperglycemia was classified into overt (pre-existing type I and II) diabetes or gestational diabetes (GDM) using the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria,[30] while hypertensive disorders of pregnancy were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP).[31] EFW and EFW centiles were calculated according to Hadlock;[32,33] birthweight according to UK 90 charts[34]; umbA and MCA according to Ciobanu et. al.[35] and FGR was defined according to ISUOG.[13]

Statistical Analysis

Participants' demographic and clinical characteristics by exposure were summarised using proportions and frequencies for categorical data and means with standard deviation (SD) for continuous data and median and interquartile range (IQR) if not normally distributed. The association between each covariate by exposure or outcome groups, was assessed using Student's t-tests (continuous variables), and Pearson chi-square ($\chi 2$) tests or Fisher's exact test (for categorical variables) as appropriate.

The unadjusted effect of each primary outcome by exposure was explored with univariable logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs). Since the multivariable analysis was to identify the effect of the primary outcomes by study arms and not develop a prognostic or diagnostic model, all identified potential confounders were included in the multivariable logistic regression model to estimate adjusted ORs (aORs) without stepwise regression. For the primary outcomes, covariates associated with both exposure and outcome at $P<0.1$ were included in multivariable analysis. For consistency across all secondary outcomes, covariates associated with the exposure at $P<0.1$ were included in the multivariable analysis (maternal age at childbirth, body mass index, ethnicity, smoking at any point during pregnancy, current illicit substance use, maternal hyperglycemia and gestational age at childbirth). The place of care was not included in the models because it was deemed on the causal pathway. All multivariable models also included time so that the effect of the exposure was adjusted for underlying trends in the data.[36] It was not possible to explore more complex interrupted time series models because most of the study outcomes were rare and the study period could only be disaggregated into a small number of time points.[36] Finally, a sensitivity analysis was conducted by handling missing data with multiple imputations (Appendix 1).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guided the study reporting. All statistical analyses were carried out in Stata MP (Version-16.1, Stata Corp., College Station, TX, USA).

Sample Size Considerations and Power Analysis

With a fixed sample size of just over 18,500 women in each of the study arms, and the estimated prevalence of extended perinatal mortality, CAPO-1 and expedited birth in the pre-exposure group being 2.0/1000 births, 3.0/1000 and 35% respectively, the calculated ranges of ORs detectable with 80% power at P<0.05 were: ≤0.41 or ≥1.82, ≤ 0.54 or ≥ 1.62 and ≤ 0.96 or ≥ 1.04, respectively.

Results

During the study period, 37267 eligible women were included: 18636 pregnancies before and 18631 pregnancies after the policy of universal ultrasound (Figure-1). Table-1 summarises the socio-demographic and pregnancy characteristics. Post-exposure, women had a slightly higher mean age and BMI, more had gestational diabetes and more cases of illicit substance use, but slightly fewer smoked and more gave birth outside a consultant-led unit.

Pre-exposure, 6605 (35.4%) had an ultrasound from 35^{+0} weeks compared with 18459 (99.1%) after. The ACGV was calculated in 4502 (24.2%) before, and in 18146 (97.4%) after). The CPR was calculated in 439 (2.4%) before, and in 17988 (96.6%) after (Table S2).

Table-2 summarises perinatal outcomes in the pre-and post-exposure groups. Extended perinatal death changed from 1.7/1000 births to 1.2/1000 (OR 0.72; 95%CI 0.42-1.23). CAPO-1 (extended perinatal mortality or encephalopathy Grade 2-3) from 2.9/1000 to 1.9/1000 total births (OR 0.67; 95%CI 0.44-1.02). Adjustment including for other covariates and time altered the point estimates little, but widened the confidence intervals. There was an increase in expedited births from 35.2% to 37.7%, but this was attenuated after adjustment for time and covariates. The proportion affected by CAPO-2 (a replication of Sovio et al[7]) changed little (9.2/1000 to 8.7/1000 total births); those affected by CAPO-3 (a replication of the IRIS study)[8] appeared to reduce (24.6/1000 to 21.4/1000 total births) but these were not significant after adjustment for time and covariates. No significant differences were found for other perinatal or neonatal outcomes.

Post-exposure, 1643 (8.9%) were 'screen positive' women at the growth scan and 1372 (7.4% of the OxGRIP group) were seen in the fetal medicine clinic, an increase of 124% (Table S2). Of those not seen, 82 gave birth first, 135 were referred and managed without a repeat ultrasound and 54 were not referred. One of these unreferred 'screen positive' babies was stillborn at 39 weeks and weighed <10th-centile. The other three deaths in 'screen positive' pregnancies had expedited births and were neonatal deaths, as a result of hypopglycaemia, late onset-Group B streptococcus (GBS), and sudden infant death syndrome (SIDS). All other 19 (82.6%) deaths during the OxGRIP period were 'screen negative'; 4 of these babies had a birthweight <10th centile.

Table 3 summarises changes in SGA and FGR detection pre- and post-OxGRIP. The detection of birthweight<10th-centile using EFW<10th-centile increased little, from 25.7% to 31.4%; the detection of birthweight<3rd-centile using EFW<3rd-centile increased from 21.6% to 26.9%. This was because, despite the increase in the number of scans, the proportion that had an EFW<10th or 3rd-centile dropped considerably: for the former from 10.7% to 4.1%.

Intervention paradox prevents calculation of screening performance of the referral criteria for mortality, but this is presented for SGA (Table 4). Where 'screen positive' for FGR, as opposed to merely EFW <10th or <3rd centiles, the detection rates of birthweight <10th-centile and <3rd-centile were 40.5% and 57.2%, respectively, albeit for a loss of specificity.

Table S3 presents secondary maternal outcomes. The small increase in expedited birth (Table-2) was due to increases in both pre-labour caesarean section (10.4% to 12.0%) and induction of labour (24.8% to 25.7%), but after adjustment neither was significant. Although significantly fewer women (19.1% to 17.1%) gave birth from 37^{+0} to 38^{+6} weeks, this observed increase was also entirely attenuated after adjustment for time. Significantly more women gave birth at ≥41week.

Discussion

Main findings

This before and after 'real-life' study describes perinatal outcomes subsequent to the introduction of a universal late third-trimester ultrasound-based screening programme for fetal growth restriction in a single large maternity unit. The relatively large reductions in the odds of 'extended perinatal mortality' (27%) and 'mortality or serious morbidity' (33%) were not statistically significant and the analysis was underpowered. Small increases in expedited birth, both pre labour caesarean and labour induction, were more likely due to underlying trends. Surprisingly, the observed 10.5% reduction in early term birth was also not significant after adjustment for covariates and time. The increase in detection of birthweight (<10th-centile) using EFW alone was modest but sensitivity was greatly increased with the addition of other scan parameters used as referral criteria.

Strengths and Limitations

Our low stillbirth rate was lower than the 3.14/1000 for Oxfordshire (2019).[2] In this analysis, we used congenitally normal births > 36^{+6} weeks. MBRRACE-UK data show that 25% of stillbirths are born at term: our rate is consistent with this.[2] The principal limitations are 1) the size of the cohort which was inadequate to detect alterations in rare outcomes and 2) that causality is unproven even after adjustment. Often, RCTs require intense resources and unlike 'real-life' studies, their findings apply only when the trial conditions are recreated. Furthermore, an intervention in some women could affect others, by diversion of resources and staff, factors repeatedly cited as contributory factors to perinatal loss.[2] The mere description of changes subsequent to a routine late ultrasound in this study is, therefore, important. Nevertheless, the findings could be due to unit-level or national trends and it is for this reason we also adjusted for covariates and time. However, 18 months of the time analysed before the introduction of OxGRIP was part of a national stillbirth initiative[37], with a subsequent 20% reduction in incidence[38] Indeed, the principal component of the national initiative was probably increased ultrasound, and induction; others (e.g. fetal movement initiatives) are unsupported by evidence[39] or changed little (e.g. smoking).

Interpretation

Previous studies of routine late pregnancy ultrasound have not been encouraging. In a systematic review of eight trials and 30675 participants, Bricker et. al. found no benefit to routine growth ultrasound (RR perinatal mortality-1.01, 95CI 0.67-1.54).[21] However, this review covered gestations from 24 weeks, Doppler and growth velocity were not considered and the management of screen positives was unspecified. Despite its size, the meta-analysis was still underpowered.[40] The IRIS study tested two scans in 13046 low-risk pregnancies[8]. Doppler was not considered, and the management protocol was unclear. Our findings was similar to the IRIS study's results (replicated as our CAPO-3).

1. Rates of adverse perinatal outcomes

Improvements in outcome may have been limited because the cause of perinatal deaths is heterogeneous, and the intervention would only address placental failure. Our reductions in extended mortality and the composite CAPO-1 may be due to chance, which could not be excluded due to limited statistical power. The management algorithm of screen positive fetuses was effective, with no stillbirths in the referred group, but one death that could be attributed to the failure to refer the woman appropriately. The problem was sensitivity, with 19/23 (82.6%) post-intervention deaths having screened negative. Part of this may be due to our reliance on categorical cut-offs, rather than continuous variables, for instance a pregnancy where the EFW was on the 11th-centile and the CPR on the 6th would have screened negative. It also reflects the limited predictive value of ultrasound and the inaccuracy of EFW estimation.

2. SGA and FGR detection

Despite the move from clinically indicated to universal ultrasound, the detection rate of birthweight<10th-centile increased little, from 25.7% to 31.4%, when using EFW<10th-centile as screen positive. That of birthweight <3rd-centile was 21.6% to 26.9%. Given the unselected nature of a universal scan, the percentage of screen positive scans (EFW<10th-centile) decreased from 10.7% to 4.1% (Table-3) following OXGRIP implementation. With the increase in scans performed, a reduction in the percentage of EFW<10th-centile was expected, but the rate of this was only 4.1%, against a UK90 incidence of birthweight<10th centile of 7.2%, and so increases in detection rate would be limited.[41] Sovio et al.[7]

previously reported a large increase in detection of birthweight <10th-centile following universal ultrasound, from 20% to 57%. Yet their percentage of screen positive scans (EFW<10th-centile) paradoxically increased in their universal scan group (14.4%) compared to their selective scan group (8.2%), which is hard to explain. Whatever the reason, it is expected that a higher screen positive rate will also be associated with higher detection rate, and higher screen positive rates could contribute to unnecessary intervention. It is also notable that others also report modest detection rates with universal scanning.[8,42]

The contribution of our detection rates can be seen: there were 5 deaths in the universal scan period who had a birthweight<10th-centile: 4 had an EFW >10th-centile. This also reflects the limited contribution of SGA to serious adverse outcomes: SGA detection is less important than that of FGR. The criteria for being 'screen positive', and therefore referred, were adapted from ISUOG Guidelines.[13] but did also include all where the EFW was <10th centile. The importance of growth velocity is emphasized in these and by Sovio et al.[7] Our assessment of growth velocity as in the methods was simplistic but easier for sonographers. The umbA-PI and CPR were also used because these have been shown to be independent of EFW in predicting adverse outcome,[14,43] with CPR modestly predicting adverse outcomes even in appropriately grown fetuses[15]. It is notable how much better our detection of low birthweight appears when our criteria for referral, which included other scan parameters, are used, albeit for a loss of specificity Table 4). Indeed, any improvement in adverse outcomes is likely to have been due to the identification of FGR, as opposed to SGA fetuses.[44] An argument could be made for routinely assessing these factors at third-trimester growth scans.

3 Rates of interventions

Reporting perinatal mortality is of limited value if intervention is not considered. Routine early-term induction reduces perinatal mortality[45] but infant mortality,[16,17] and childhood neurodevelopmental complications,[18–20] are higher than after birth at 39-41 weeks. This is reflected in the UK's rising NNU admission rate,[38] itself ironically a national target[46]. Expedited birth may therefore cause considerable but unmeasured harm in many, for the benefit of few. Expedited birth also limits choice, and by creating

additional workload,[38] may create risk.[47] Our third primary outcome, therefore, assessed expedited birth, either by induction of labour or pre-labour caesarean section. This rose 7.1%, from 35.2% to 37.7%. The 3.6% increase in induction is lower than the 16.1% reported by Heinrichs et al.[8] and the 20% increase[38] reported with the English Saving Babies Lives Initiative and indeed following adjustment for covariates and time, was not statistically significant. Further, early-term birth, with the potential to cause most harm[16–20], did not increase. This is likely to be due to secondary assessment and management at the 'growth' clinic, but this required increased resource in addition to that required for universal scanning.

Surprisingly, more pregnancies reached 41 and 42 weeks, when it is known that expediting birth at 41 weeks reduces perinatal mortality.[48] Nevertheless, there were no deaths in the intervention period and only one with CAPO-1 was born after 41^{+0} weeks. It is unclear why this change occurred. Perhaps the scan provided reassurance; the unit policy of offering induction of labour by 42^{+0} weeks remained unchanged.

Conclusion

A universal scan programme can be successfully implemented, but the impact on serious adverse outcomes remains unclear. Detection of SGA remains poor, but the use of markers of FGR improves detection considerably. Protocol-driven management of 'screen positives' minimises intervention but creates further workload. The limited change in adverse perinatal outcomes is not primarily because of poor birthweight (<10^{th}-centile) detection rates. It is likely to be because scan parameters, particularly when assessed once, are not the only risk factors for adverse outcome: demographic and clinical factors and biomarkers also matter.[49] This points to the need for predictive models. Limited versions exist but are at high risk of bias and have not been rigorously tested[50]. This needs urgent attention and the Tommy's app[51] is welcomed in this regard. In combination with the few preventative measures available, better underlying health and resources, addressing human factors, and established interventions such as post-dates induction, perinatal mortality can be reduced further. Importantly, this must not lead to a shortening of the already brief human gestation, as long-term morbidity could be the price of reduced perinatal mortality.

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Disclosure of Interests

None

Contribution to authorship

AKA and LI conceptualized and designed the study; CI, AC and LI were involved in performing the intervention; AKA performed the data analysis; All authors interpreted the results; AKA drafted the article; All the authors reviewed, approved and are accountable for the final version for publication.

Ethics Committee approval

NHS Health Research Authority ethical approval for this analysis was granted on 27/07/2017 (IRAS project ID 222260; REC reference 17/SC/0374).

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Table Legends

Supplementary Figures and Tables Legends

Table 1: Demographic and pregnancy characteristics before and after universal late third trimester ultrasound

Variable	Pre-OxGRIP n = 18636	OxGRIP n = 18631	P -value
Maternal Age - years, median (IQR)	31.0 (27.0 – 35.0)	31.0 (28.0 – 35.0)	0.003
Maternal Age (years, n (%))			< 0.0001
< 20	440 (2.4)	320 (1.7)	
20 – 34	13311 (71.4)	13246 (71.1)	
≥ 35	4885 (26.2)	5065 (27.2)	
Body mass index - kg/m^2, median (IQR)	24.1 (21.5 - 27.8)	24.3 (21.6 – 28.1)	0.001
Body Mass Index - kg/m^2, n (%))			
Underweight (<18.5)	534 (2.9)	542 (2.9)	< 0.0001
Normal (18.5 - 24.9)	9896 (53.1)	9785 (52.5)	
Overweight (25.0 - 29.9)	4687 (25.1)	4827 (25.9)	
Obesity (≥ 30.0)	2956 (15.9)	3310 (17.8)	
Data Missing	560 (3.0)	167 (0.9)	
Ethnicity, n (%)			< 0.0001
White	14773 (79.3)	14844 (79.7)	
Black or African Descent	392 (2.1)	385 (2.1)	
Asian or Asian Descent	1322 (7.1)	1444 (7.7)	
Mixed or others	497 (2.7)	609 (3.3)	
Data Missing	1652 (8.8)	1349 (7.2)	
Parity, n (%)			0.141
0	7982 (42.8)	8161 (43.8)	
1	6988 (37.5)	6779 (36.4)	
2 – 4	3506 (18.8)	3538 (19.0)	
≥ 5	160 (0.9)	153 (0.8)	
Deprivation (IMD Quintile, n (%))			0.327
1 (Most deprived)	999 (5.4)	968 (5.2)	
2	1758 (9.4)	1709 (9.2)	
3	3087 (16.6)	3118 (16.7)	
4	5313 (28.5)	5224 (28.0)	
5 (Least deprived)	7471 (40.1)	7596 (40.8)	
Data Missing	8 (0.0)	16 (0.1)	
Smoking at any point in pregnancy, n (%)	1899 (10.2)	1842 (9.9)	< 0.0001
Missing	805 (4.3)	274 (1.5)	
Current illicit substance use, n (%)	63 (0.3)	126 (0.7)	< 0.0001
Missing	611 (3.3)	1015 (5.4)	
Assisted conception - In-vitro fertilisation, n (%)	312 (1.7)	329 (1.8)	0.496
Any PIH or preeclampsia, n (%)	932 (5.0)	905 (4.9)	0.522
Maternal Hyperglycaemia, n (%)			
Type 1/ 2 diabetes	93 (0.5)	85 (0.5)	< 0.0001
Gestational diabetes Mellitus	852 (4.6)	1086 (5.8)	
Place of birth, n (%)			
Consultant-led unit	15076 (80.9)	14264 (76.6)	< 0.0001
Midwifery-led Unit	3087 (16.5)	3818 (20.5)	
Home	406 (2.2)	410 (2.2)	
Birth before arrival	67 (0.4)	139 (0.7)	
Gestational age at birth – weeks, median (IQR)	40.0 (39.1 – 40.9)	40.1 (39.1 – 41.0)	<0.0001
Sex of baby, n (%)			
Female	9073 (48.7)	9089 (48.8)	0.595
Male	9563 (51.3)	9541 (51.2)	
Missing/ not known	0 (0.00)	1 (0.0)	

Table 2: Perinatal outcomes before and after universal late third trimester ultrasound

Variable	pre-OxGRIP events/number in group	OxGRIP events/number in group	Unadjusted Odds Ratio (95% Confidence Intervals)	Adjusted Odds Ratio (95% Confidence Intervals)
Primary Outcomes				
Extended perinatal mortality (n, per 1,000 total births)	32/18636 (1.7/1000)	23/18631 (1.2/1000)	0.72 (0.42 – 1.23)	0.53 (0.18 – 1.56) [a,b]
Composite adverse perinatal outcome -1(CAPO 1) (n, per 1000 total births) [c]	54/18636 (2.9/1000)	36/18631 (1.9/1000)	0.67 (0.44 – 1.02)	0.71 (0.31 – 1.63) [a,d]
Expedited birth - pre-labour caesarean section or induction (n, %)	6564/18636 (35.2)	7026/18631 (37.7)	1.11 (1.07 – 1.16)	0.98 (0.90 – 1.07) [a,e]
Secondary Outcomes				
Composite adverse perinatal outcome -2 (CAPO 2) (n, per 1000 total births) [f]	172/18636 (9.2/1000)	163/18631 (8.7/1000)	0.95 (0.76 -1.17)	1.04 (0.66 – 1.63) [g]
Composite adverse perinatal outcome -3 (CAPO 3) (n, per 1000 total births) [h]	458/18636 (24.6/1000)	399/18631 (21.4/1000)	0.87 (0.76 - 0.99)	1.20 (0.90 – 1.59) [g]
Stillbirth (n, per 1,000 total births)	25/18636 (1.3/1000)	16/18631 (0.9/1000)	0.64 (0.34 – 1.20)	0.33 (0.08 – 1.28) [g]
Perinatal death (n, per 1,000 total births)	31/18636 (1.7/1000)	20/18631 (1.1/1000)	0.64 (0.37 – 1.13)	0.33 (0.10 – 1.14) [g]
Apgar score <7 at 5 minutes (n, %) [i]	194/17940 (1.1)	166/18175 (0.9)	0.84 (0.68 – 1.04)	0.90 (0.58 – 1.39) [g]
Hypoxic Ischaemic Encephalopathy - ≥ Grade II (n, %) [j]	27/18611 (0.2)	15/18615 (0.1)	0.56 (0.30 – 1.04)	0.92 (0.25 – 3.36) [g]

[a] Adjusted for time and covariates associated with both exposure and outcome at P < 0.1
[b] Adjusted for time, gestational age at birth; and no effect modification by gestation age ≥ 41 weeks.
[c] Composite adverse perinatal outcome (CAPO) 1 - Any of extended perinatal mortality or livebirth associated with hypoxic-iscahemic encephalopathy (HIE II or III) <72 hours after birth
[d] Adjusted for time, gestational age at birth and maternal hyperglycaemia, and no effect modification by gestation age ≥ 41 weeks
[e] Adjusted for time, maternal age at birth, body mass index, ethnicity, smoking, illicit substance use, and maternal hyperglycaemia
[f] Composite adverse perinatal outcome (CAPO 2) - Any of stillbirth, term livebirth associated with neonatal death, any HIE, use of inotropes, need for mechanical ventilation, severe cord acidosis (arteria pH < 7.0)[7]
[g] Adjusted for time, maternal age at childbirth, body mass index, ethnicity, smoking at any point during pregnancy, current illicit substance use, maternal hyperglycaemia and gestational age at childbirth
[h] Composite adverse perinatal outcome (CAPO 3) - Perinatal death, Apgar score <4 at five minutes, Impaired consciousness (coma, stupor, or decreased response to pain), cord acidosis (arterial cord pH any seizures, assisted ventilation by endotracheal tube for more than 24 hours starting within 72 hours of birth, septicaemia confirmed by blood culture, necrotising enterocolitis confirmed by radiography, s or autopsy and any hypoxic-ischaemic encephalopathy[8]
[i] Stillbirths [Pre-OxGRIP (n =25) vs OxGRIP (n =16)] and those without APGAR scores [pre-OxGRIP (n =671) vs OxGRIP (n = 440)] excluded

Table 3: Small for gestation age and fetal growth restriction detection

Variable	pre-OxGRIP events/number in group (%)	OxGRIP events/number in group (%)	Unadjusted Odds (95% Confidence Intervals)	[a] Adjusted Odds Ratio (95% Confidence Intervals)
Birthweight < 10th centile [b]	1396/18636 (7.5)	1340/18631 (7.2)	0.96 (0.89 – 1.03)	0.96 (0.81 – 1.13)
Birthweight < 3rd centile [c]	297/18636 (1.6)	264/18631 (1.4)	0.89 (0.75 – 1.05)	0.83 (0.59 – 1.18)
Birthweight <10th centile detection using EFW <10th centile at ≥ 35+0 weeks [b]	359/1396 (25.7)	421/1340 (31.4)	1.32(1.12 – 1.56)	1.52 (1.02 – 2.28)
Birthweight <3rd centile detection using EFW <3rd centile at ≥ 35+0 weeks [c]	64/297 (21.5)	71/264 (26.9)	1.34 (0.91 – 1.97)	0.81 (0.28 – 2.37)
Estimated fetal weight (EFW) <10th centile at ≥35+0 (per scan performed) [c]	705/6605 (10.7)	762/18459 (4.1)	0.36 (0.32 – 0.40)	0.50 (0.40 -0.63)
Estimated fetal weight (EFW) <10th centile at ≥35+0 (% of all pregnancies) [d]	705/18636 (3.8)	762/18631 (4.1)	1.08 (0.98 – 1.20)	1.31 (1.05 – 1.64)
Estimated fetal weight (EFW) <3rd centile at ≥35+0 (per scan performed) [d]	201/6605 (3.0)	225/18459 (1.2)	0.39 (0.32 – 0.48)	0.38 (0.25 – 0.57)
Estimated fetal weight (EFW) <3rd centile at ≥35+0 (% of all pregnancies) [d]	201/18631 (1.1)	225/18631(1.2)	1.12 (0.93 – 1.36)	0.88 (0.58 – 1.33)
Fetal growth restriction (per pregnancy scanned) [e]	299/6605 (4.5)	408/18459 (2.2)	0.48 (0.41 – 0.55)	0.49 (0.35 – 0.67)
Fetal growth restriction (% of all pregnancies) [e]	299/18636 (1.6)	408/18631 (2.2)	1.37 (1.18 – 1.60)	1.19 (0.86 – 1.64)

[a] *Adjusted for time maternal age at childbirth, body mass index, ethnicity, smoking at any point during pregnancy, current illicit substance use, maternal hyperglycaemia and gestational age at childbirth*
[b] *Denominator is Birthweight < 10th centile (UK90)*
[c] *Denominator is Birthweight < 3rd centile (UK90)*
[d] *EFW using Hadlock formula for head circumference, abdominal circumference and femur length*
[e] Fetal growth restriction defined using Delphi criteria[13] Abdominal circumference (AC) /estimated fetal weight (EFW) < 3rd centile or at least 2 out of the following:
1)AC/EFW < 10th centile, 2) AC/EFW crossing centiles >2 quartiles on non-customized growth centiles,
3) cerebroplacental ratio (CPR) < 5th centile or umbilical artery pulsatility index (UA-PI) > 95th centile

Table 4: Screening performance of universal late third trimester ultrasound

Variable	Accuracy Test	Universal Scan Group
Birthweight <10th centile detection using study screen positive criteria at ≥ 35+0 weeks [a,b]	Sensitivity (%)	40.5 (37.9 – 43.2)
	Specificity (%)	93.6 (93.3 – 94.0)
	Positive predictive value (%)	33.0 (30.8 – 35.4)
	Negative predictive value (%)	95.3 (95.0 – 95.6)
	Positive likelihood ratio	6.4 (5.8 – 7.0)
	Negative likelihood ratio	0.635 (0.608 – 0.664)
	Area under the receiver operating characteristics curve	0.671 (0.658 – 0.684)
Birthweight <3rd centile detection using study 'screen positive' criteria at ≥ 35+0 weeks [a.c]	Sensitivity (%)	57.2 (51.0 – 63.2)
	Specificity (%)	91.9 (91.5 – 92.3)
	Positive predictive value (%)	9.2 (7.8 – 10.7)
	Negative predictive value (%)	99.3 (99.2 – 99.5)
	Positive likelihood ratio	7.0 (6.3 – 7.9)
	Negative likelihood ratio	0.466 (0.405 – 0.536)
	Area under the receiver operating characteristics curve	0.745 (0.715 – 0.775)

[a] 'screen positive' criteria refers to any of EFW <10th centile, UmbA PI >95th centile, cerebro-placental ratio <1.1, or a >40 centile points abdominal circumference deceleration compared to the 20-week scan

[b] Denominator is Birthweight < 10th centile (UK90)

[c] Denominator is Birthweight < 3rd centile (UK90)