OBSTETRICS

Single versus longitudinal scans in the third trimester: a multicenter randomized clinical trial on screening for late-onset intrauterine fetal growth restriction (The RCT on Evaluation of LAte Iugr Screening study)

Alessandra Familiari, MD; Tamara Stampalija, MD, PhD; Federico Prefumo, MD, PhD; Giulia di Marco, MD; Maria Giulia Ferrante, MD; Elisa Bevilacqua, MD, PhD; Giulia Zamagni, MD, PhD; Lorenzo Monasta, MD, PhD; Grazia Tiralongo, MD; Herbert Valensise, MD, PhD; Maddalena Morlando, MD, PhD; Laura Sarno, MD, PhD; Daniele Di Mascio, MD, PhD; Ilenia Mappa, MD; Giuseppe Rizzo, MD, PhD; Silvia Visentin, MD, PhD; Anna Fichera, MD, PhD; Tatjana Radaelli, MD; Baskaran Thilaganathan, MD, PhD; Giovanni Scambia, MD, PhD; Tullio Ghi, MD, PhD; Enrico Ferrazzi, MD, PhD

BACKGROUND: Undiagnosed fetal smallness is strongly associated with adverse perinatal outcomes. Despite robust evidence that late third trimester ultrasound improves small for gestational age detection, the question of whether routine ultrasound assessment in late pregnancy can improve perinatal outcome remains unresolved.

OBJECTIVE: The objective of the study was to assess whether the addition of a 35 to 37–week scan in low-risk pregnancy would improve the detection of small for gestational age at birth without increasing cesarean section rates or neonatal morbidity.

STUDY DESIGN: Open label multicentric randomized trial recruiting nulliparous low-risk pregnant women in 10 Italian centers between January 2021 and March 2023. Patients were randomly assigned at midtrimester scan to either routine care (single scan at 28–32 weeks) or intervention (routine care plus additional scan at 35–37 weeks). The primary endpoint was prenatal detection of small for gestational age neonate with birthweight <10th centile. Predefined secondary outcomes included detection of severe fetal smallness defined as birthweight <third centile, cesarean section rate, composite mild/severe adverse neonatal outcome, and intact neonatal survival. The study is registered at ClinicalTrials.gov (NCT05787054) on the first of March, 2023.

RESULTS: The antenatal detection of small for gestational age birth was significantly higher in the intervention (9/46, sensitivity 19.5%) vs routine care (0/28, sensitivity 0%) arms of the trial (P=.011). False positive rate for the intervention for the routine care arms were 1.7% and 2.0%, respectively. The total cesarean section rate was unchanged (odds ratio, 0.89; 95% confidence interval, 0.63–1.26) and the neonatal intensive care unit admission rate was significantly lower for patients allocated to have a scan at 35 to 37 weeks (3.8% vs 1.0%; odds ratio, 0.27 [95% confidence interval, 0.09–0.80]). Composite adverse neonatal outcomes and intact neonatal survival rates were not significantly different between 2 groups.

CONCLUSION: In a low-risk population performing an additional ultrasound scan at 35 to 37 weeks increases the detection of small for gestational age at birth and reduces the rate of neonatal intensive care unit admission without affecting rates of labor induction or total cesarean birth.

Key words: fetal smallness, intrauterine growth restriction, late fetal growth restriction, third trimester screening

Introduction

Fetal smallness is the strongest known antenatal risk factor for adverse perinatal outcomes such as stillbirth, neonatal mortality, and severe neonatal morbidity including hypoxemia ischemic encephalopathy and subsequent cerebral palsy.[1–6] This is particularly evident when fetal smallness is undiagnosed before birth, as occurs in approximately 50% of stillbirth cases at term, with evidence of risk reduction on antenatal ultrasound detection of small for gestational age (SGA) fetuses.[2–6] Early third trimester routine ultrasound in a low-risk population showed low sensitivity in the detection of SGA birth.[7,8] However, high-quality evidence from blinded observational, randomized control trial and systematic review studies has more recently demonstrated that late third trimester ultrasound has improved accuracy for SGA birth than routine care or early third trimester ultrasound, with detection rates reaching up to 60% in low-risk pregnant populations.[9–11]

Despite evidence linking fetal smallness to severe adverse pregnancy outcomes and late third trimester ultrasound to improved detection of SGA fetuses, many national and international guidelines do not recommend the use of routine late third trimester ultrasound assessment in low-risk pregnancy.[12–14] The public health policy rationale for withholding the offer of late third trimester ultrasound in low-risk pregnancy is over concern that the false positive rate for SGA detection on ultrasound will result in increased rates of cesarean section birth and iatrogenic early term birth for a diagnosis of SGA leading to neonatal morbidity and neonatal intensive care unit (NICU) admission.[11,15,16] The randomized controlled trial (RCT) on Evaluation of Late Intrauterine Growth Restriction Screening (RELAIS trial) was designed to test the hypothesis that the addition of a late third trimester ultrasound in low-

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2025.11.027

Click Supplemental Materials and Video under article title in Contents at ajog.org

AJOG at a Glance

Why was this study conducted?

This study was set up to assess whether the addition of a 35 to 37−week scan in low-risk pregnancy would improve the detection of small for gestational age at birth without increasing cesarean section rates or neonatal morbidity.

Key findings

The addition of an ultrasound scan at 35 to 37 weeks significantly increases the antenatal detection of small for gestational fetuses at birth compared to routine care inclusive of only one ultrasound scan at 28 to 32 weeks. Moreover, this policy was associated with a 3-fold reduction in neonatal intensive care unit admission rate without affecting rates of induction of labor, cesarean section, or adverse neonatal outcomes.

What does this add to what is known?

There is evidence of clinical benefit with a policy of universal screening for fetal growth disorders at 35 to 37 weeks in low-risk pregnancies.

risk pregnancy would improve the detection of SGA birth without increasing rates of labor induction, cesarean section, or neonatal morbidity.

Methods

Study design and participants

The RELAIS study was an open-label multicenter RCT. Nulliparous pregnant women, with singleton pregnancy and no risk factors for fetal growth disorders or placental insufficiency, were recruited in 10 Italian hospitals (Supplemental Table 1). All recruiting hospitals were referral centers also providing a screening ultrasound for fetal growth disorders. Patients were considered eligible if they had an 11 to 13−week dating ultrasound and routine mid-trimester anomaly ultrasound assessments. Exclusion criteria were fetal anomalies, major maternal comorbidities including chronic hypertension, congenital heart disease, diabetes, psychiatric disorders requiring medications, obesity and maternal immune or thrombophilic disorders, assisted reproductive technique pregnancies, maternal immune or thrombophilic disorders, and high risk for preeclampsia or maternal serum pregnancy-associated plasma protein A <0.2 multiples of the median. If at 19 to 22 weeks fetal abdominal circumference and/or estimated fetal weight (EFW) were below the fifth centile, the women were excluded from the study and monitored according to the local high-risk protocol. This study was designed to generate level 1 evidence of diagnostic effectiveness.[17] The reporting of this study follows CONsolidated Standards Of Reporting Trials guidelines. Ethics approval for the study was obtained by the coordinating center (Number 12315/19, ID1909), and ancillary approval was obtained from each participating center. The trial was registered on clinicaltrial.gov https://clinicaltrials.gov/study/NCT05787054.

Randomization and masking

Women were recruited at the routine mid-trimester ultrasound at each participating center. After written informed consent, they were randomly assigned in a 1:1 ratio through a centrally provided Research Electronic Data Capture web application. The block size of 10 was generated using an online number randomization tool and was stratified by participating site to ensure a balanced distribution between study groups. At recruitment, if fetal biometry and anatomy were normal, patients were randomized to either the routine care (including a single scan at 28−32 weeks) or the intervention (routine care plus an additional scan at 35−37 weeks). The assignment was unmasked: patients, research staff, and medical teams were aware of the study group assignment after randomization. Pseudo-anonymized study data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at Fondazione Policlinico Universitario A. Gemelli, IRCCS (https://redcap-irccs.policlinicogemelli.it/).[18] Data processing took place in compliance with current European legislation regarding General Data Protection Regulation.

Procedures

The ultrasound was performed by experienced physicians—board-certified obstetrician-gynecologists with specialized training in obstetric ultrasound—with ultrasound biometry and Doppler parameters measured according to a standardized protocol.[19,20] Fetal biometry and EFW were converted to percentiles using an international reference standard derived from low-risk pregnancies from optimally healthy women who had a normal pregnancy outcome, the INTERGROWTH-21st.[21] SGA fetuses were defined as those with an ultrasound EFW <10th centile. The quality of ultrasound and Doppler measurements were audited annually, stratified by center, by random selection of images for quality assessment. Screen positive cases from both trial arms were clinically managed according to the local policy at each recruiting center. All women who developed a pregnancy complication which required intensive surveillance or delivery before the early growth scan were excluded from both arms of the study. A modified intention-to-treat analysis was performed, including all participants who were randomized, provided informed consent, and had complete outcome data, excluding only those who withdrew consent or were later excluded due to predefined medical conditions.

Outcomes

The primary outcome of the trial was the antenatal detection of an SGA neonate with a birthweight (BW) <10th centile based on neonatal reference standard charts (adjusted for sex)[22] comparing 2 different screening strategies: a single 28 to 32 weeks of scan (the routine care arm) and a longitudinal scan policy providing an extra scan at 35 to 37 weeks (the interventional arm). The prespecified secondary outcomes were detection of severe fetal smallness defined as BW <third centile, cesarean section rate, composite mild adverse neonatal outcome (Apgar score at 5 minutes <7, umbilical artery pH <7.10 or base deficit >8 mmol/L, and NICU admission), composite severe adverse perinatal outcome (stillbirth, neonatal death at term, hypoxic ischemic encephalopathy, use of inotropes, need for mechanical ventilation, or severe metabolic acidosis defined as umbilical artery pH <7·0 and base deficit >12 mmol/L), and intact neonatal survival (defined as any neonatal morbidity resulting in a neonatal intervention or delay in routine neonatal discharge from hospital).

Statistical analysis and sample size

Sample size calculation was determined a priori using published data on sensitivity of ultrasound for identifying SGA (BW <10th centile) in the 2 study arms. For the 28 to 32 scan group, sensitivity was based on results by Roma et al (22.5%).[9] The results published by Sovio et al were instead taken for the "longitudinal" group (57% sensitivity)[10] because the design of the Pregnancy Outcome Prediction (POP) study included both an early and third trimester scan. Our trial was powered to detect a clinically relevant difference of approximately 20 percentage points in sensitivity between the 2 strategies, assuming an SGA prevalence of 10%, considering a confidence level of 95% (1-alpha) and an 80% power (1-beta), and a one-to-one ratio between the routine care and additional 35 to 37—week scan group. According to Fleiss[23] (n=(Z^2 * p * (1-p))/E^2), each arm should include 32 women with SGA pregnancies or a total of 64 women for the trial arms combined. SGA fetuses represent 10% of the total population, resulting in a total sample size of 640 women. Assuming a 10% of drop-out and incomplete data rate, the final trial sample size was calculated as 704 patients. Demographic and maternal characteristic variables were collected to describe the study population. Categorical variables were reported as counts and percentages, while continuous variables as mean and standard deviation or median and interquartile range, based on the result of the Shapiro-Wilk normality test. Between-group differences were evaluated with the Chi-square test (or the Fisher's exact test, when appropriate) in case of categorical variables and with Student's *t* test (or the Wilcoxon Mann-Whitney test) in case of continuous variables. The effect of the protocol on the outcomes of interest was assessed using binary or multinomial regression, based on the type of outcome. To assess the relationship between antenatal and postnatal weight centiles, a robust regression model was developed to estimate the BW centile based on the EFW centile at 28 to 32 weeks and at 35 to 37 weeks. A nonzero intercept was considered indicative of fixed differences (ie, systematic bias) and slope deviating from 1 as evidence of proportional differences (ie, proportional bias). Statistical significance was set at 0.05. All the analyses were carried out using Stata software, version 18.

Role of the funding source

This study was conducted on the behalf and with the support of the Italian Society of Obstetrics and Gynecology (SIGO) which had no role in data analysis, data interpretation, or writing of the report.

Results

Study population

Between January 1, 2021 and March 1, 2023, 829 patients were assessed for eligibility at the time of the mid-trimester anomaly scan. 813 (98.1%) fulfilled the inclusion criteria and provided written informed consent to participate in the RELAIS trial. After randomization at a median gestational age of 20.3 weeks, 407 patients were allocated to routine care and 406 were allocated to the intervention (routine care plus an additional scan at 35—37 weeks' gestation). A total of 23 patients were excluded from the trial: 5 withdrew their consent, 16 patients were lost at follow-up, one patient had an early fetal growth restriction diagnosis before 28 weeks' gestation, and one had a vascular thrombosis with a diagnosis of unknown autoimmune disorder

TABLE 1
Demographic and patient characteristics in routine care (single scan; control) and intervention (longitudinal scans) groups of the RELAIS trial

Characteristics	Routine care: single scan at 28—32 weeks (n=396)	Intervention: additional 35 to 37—week scan (n=394)
Gestation at recruitment (wks)	20.3 (20.0—20.9)	20.3 (20.0—20.9)
Age group (y)		
18—24	30 (7.6)	31 (7.9)
25—34	276 (69.7)	261 (66.2)
34—40	90 (22.7)	102 (25.9)
Body mass index	23.1 (21.3—25.3)	23.0 (21.4—25.4)
Ethnicity		
Caucasian	368 (93.4)	370 (93.9)
Asian	10 (2.5)	10 (2.5)
African	12 (3.1)	9 (2.3)
Hispanic	4 (1.0)	5 (1.3)
Unspecified	2 (0.5)	0

Data provided as number (%) or median (IQR).

TABLE 2
Prespecified primary and secondary outcomes in routine care (single scan; control) and intervention (longitudinal scans) groups of the RELAIS trial

Outcomes	Routine care: single scan at 28–32 weeks (n=396)	Intervention: additional 35 to 37–week scan (n=394)	OR [95% CI] or *P* value
Primary outcome			
Antenatal detection rate of SGA birth (<10° centile)	0/28 (0%)	9/46 (19.5%)	**0.011**
Prespecified secondary outcomes			
Antenatal detection rate of severe SGA birth (<3° centile)	0/4 (0%)	2/9 (22.2%)	1.000
Total cesarean section (CS) rate	84 (21.1)	76 (19.3)	0.89 [0.63; 1.26]
Composite mild adverse neonatal outcome	2 (0.5)	1 (0.3)	0.50 [0.05; 5.55]
Composite severe adverse perinatal outcome	1 (0.3)	0	1.000
Intact neonatal survival	287 (76.3)	274 (74.3)	0.89 [0.64; 1.25]

Composite mild adverse neonatal outcome: Apgar score at 5 minutes <7, umbilical artery pH<7.10 or base deficit >8 mmol/L, neonatal intensive care unit (NICU) admission. *Composite severe adverse perinatal outcome*: stillbirth or term live birth associated with neonatal death, hypoxic ischemic encephalopathy, use of inotropes, need for mechanical ventilation, or severe metabolic acidosis defined as umbilical artery pH<7.0 and base deficit >12 mmol/L. *Intact neonatal survival*: neonatal survival without any morbidity or admission to NICU. Bold values indicate *P* value < 0.5.

Data provided as median (IQR) or number (%) with differences reported as odds ratios (OR) with 95% confidence intervals (95% CI) or *P* value (Fisher's exact test).

CI, confidence interval; *OR*, odds ratio; *SGA*, small for gestational age.

(Supplemental Figure 1). Table 1 shows the baseline characteristics of the 790 patients from study population with complete data. Supplemental Table 1 shows the contribution of each recruiting center.

Detection of small for gestational age at birth

At delivery, there were 28 (7.1%) and 46 (11.7%) infants with a BW <10th percentile thus meeting the SGA definition in the routine care arm and in the intervention arm, respectively. The primary outcome—the ability to prenatally diagnose SGA as BW <10th centile—was significantly higher in the intervention (9/46, sensitivity=19.5%; 95% confidence interval [CI], 9.4–33.9 and specificity=98·3% [95% CI, 96·3–-99·4]) than in routine care (0/28, sensitivity=0·0% [95% CI, 0·00–12·3], specificity=98·0% [95% CI, 95·9–-99·1]) arms of the trial (*P*=.011, Table 2). None of the 28 SGA births in the routine care group was identified prenatally and of 8 fetuses labeled as SGA at the 28 to 32–week scan, none was diagnosed as SGA at birth, indicating a 2.0% false positive rate (95% CI, 0.9–4.1). In the intervention group, 2 SGA fetuses were correctly identified at 28 to 32 weeks and 9 at 35 to 37 weeks' gestation. Six fetuses were incorrectly labeled as SGA at 35 to 37 weeks and were born with a BW >10th centile, corresponding to a 1.7% false positive rate (95% CI, 0.6–3.6).

Robust regression modeling of the BW centile based on EFW centile at 28 to 32 weeks indicated both fixed and proportional biases, with an intercept of 13.37 (*P*<.001) and slope of 0.54 (95% CI, 0.46–0.63) (*P*<.001, Figure 1). At 35 to 37 weeks, the robust regression model did not show a fixed bias (intercept=3·51, *P*=.397). The slope was 0.77 (95% CI, 0.66–0.88) (*P*<.001), indicating that BW centiles increase by 0.77 units for each one-unit increase in EFW centile. The 35 to 37–week model showed less proportional bias than the 28 to 32–week model (23% vs 46%) with no evidence of systematic bias.

Supplemental Figure 2 shows EFW plotted against gestational age (in weeks) in the study population according to the INTERGROWTH-21st (IG21) standard. A substantial proportion of the study population lies above the IG21 median, suggesting a potential miscalibration between the growth standards and the actual distribution in this population.

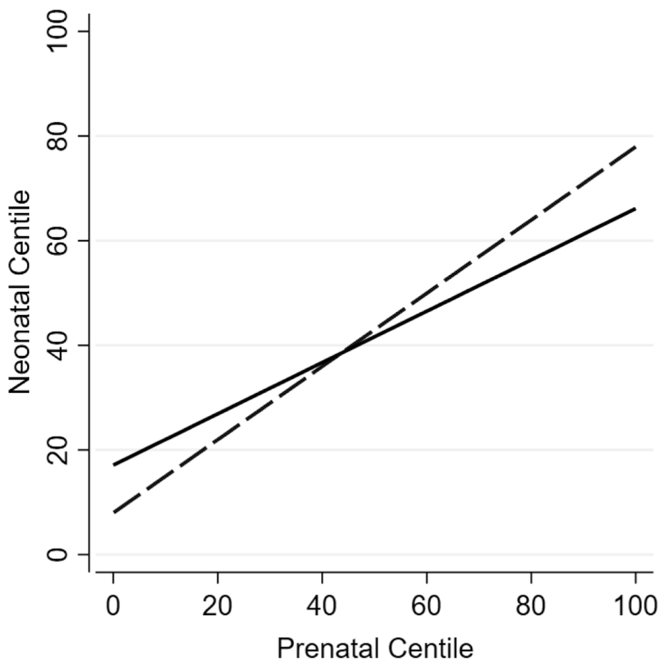
Prespecified secondary outcomes

The cesarean section rate was not significantly different between the 2 groups (Table 2: odds ratio [OR], 0.89; 95% CI, 0.63–1.26). Indications for scheduled cesarean sections were: low lying placenta, maternal request, and breech presentation. Emergency cesarean sections were performed for nonreassuring fetal heart rate, bradycardia, failure to progress, and cord prolapse. Mild/severe composite adverse neonatal outcome rates and intact neonatal survival rates were not significantly different between the 2 groups. There were 4 (1.0%) and 9 (2.3%) SGA births <third centile in the routine care and intervention groups, respectively, with no significant difference in the antenatal detection rate between trial arms (0/4 vs 2/9, *P*=1.000).

Other pregnancy outcomes

The NICU admission rate was significantly lower for patients allocated to additional scan at 35 to 37 weeks (3.8% vs 1.0%; OR, 0.27 [95% CI, 0.09–0.80]; Table 3). In this arm, there were also considerable differences in scheduled cesarean birth (OR, 0.57 [95% CI, 0.34–0.94]) and SGA cesarean birth (OR, 7.69 [95% CI, 1.66–35.58]). There were no substantial differences between

FIGURE 1
Robust regression model of prenatal birthweight vs neonatal weight centile



The intercept (13.37 vs 3.51; $P<.001$), slope (0.54 [0.46—0.63] vs 0.77 [0.66—0.88]; $P<.001$), and proportional bias (23% vs 46%) were superior at 35 to 37 weeks; 28 to 32 weeks (solid line); 35 to 37 weeks (dashed line).

groups for prevalence of induction of labor, mode of birth, gestation at birth, and rate of preterm birth (Table 3). Although BW centile did not vary between groups, the prevalence of SGA at birth was significantly higher in the intervention group (11.7% vs 71%: OR, 1.74 [95% CI, 1.06—2.220]).

Comment

This RCT conducted in low-risk pregnancies demonstrates that the addition of a late third trimester ultrasound scan at 35 to 37 weeks significantly increases the antenatal detection of SGA fetuses compared to routine care with only one ultrasound scan at 28 to 32 weeks. The increased detection of SGA birth with the 35 to 37—week scan was associated with a significant reduction in admission to the NICU, but no change in rates of induction of labor, early term birth, overall cesarean birth, or adverse perinatal outcome.

Strengths and limitations of the study

This is the first RCT assessing the value of an addition of a late third trimester scan in low-risk pregnancy for the detection of SGA at birth and perinatal outcomes. The multicenter RCT design, sample size, and routine clinical setting provide confidence in statistical power and support the generalizability of the study findings. However, an important limitation is that the study was powered to detect a difference in the sensitivity of the intervention ultrasound scan for SGA detection, but not for secondary outcomes. While some secondary outcomes showed potentially clinically relevant and statistically significant differences, the CIs were often wide, potentially limiting the precision of these estimates. Another limitation is the significant difference in SGA rate in the routine care and intervention arms of the trial, but the total number of SGA births in the study exceeded the required sample size, thereby preserving the statistical power of the study. Randomization was performed centrally, stratified by study site, and resulted in groups well balanced for all baseline maternal and obstetric characteristics, as shown in Table 1. Furthermore, the difference in SGA rate was mitigated by assessing SGA diagnosis rate and other perinatal outcomes as a function of the total number of pregnancies or SGA births in each group. The trial was open label, mandated by the fact that it was not possible to mask caregivers or patients to the intervention—an additional ultrasound scan in the late third trimester. As the intention was for clinicians to have access to the findings of the trial clinical investigation, this limitation should not have affected the study findings or applicability. The study did not stipulate the clinical management protocol after the antenatal diagnosis of an SGA fetus, introducing the possibility of bias. However, clinicians in recruiting centers generally followed international guidance with adaptations for the local clinical setting and availability of resources.[24] Moreover, the degree to which this study's findings are generalizable are defined by the population defined as "low-risk" and are not applicable to high-risk pregnancies which mandate much closer fetal monitoring.

Timing of third trimester scans for small for gestational age detection

The results of this study demonstrate that the addition of a late third trimester ultrasound scan at 35 to 37 weeks significantly increases the antenatal detection of SGA fetuses compared to routine care inclusive of only one ultrasound scan at 28 to 32 weeks. Indeed, although specificity was comparable in the 2 arms of the trial, sensitivity was significantly higher in the intervention arm with late ultrasound. The observation that a late third trimester scan is superior for SGA detection than one done in the early third trimester is consistent with data from both large national cohort studies and a previous

TABLE 3
Outcomes in routine care (single scan; control) and intervention (longitudinal scans) groups

	Routine care: single scan at 28–32 weeks (n=396)	Intervention: additional 35 to 37–week scan (n=394)	OR [95% CI] or *P* value
Timing of birth			
All births (wks)	39 (38–40)	39 (38–40)	1.01 [0.47; 2.14]
Preterm (<37 wks) birth rate	14 (3.5)	14 (3.5)	
Vaginal birth			
Induction of labor	102 (25.8)	84 (21.3)	0.78 [0.56; 1.09]
Vaginal birth	297 (75.5)	310 (78.7)	1.23 [0.88; 1.71]
Spontaneous vaginal birth	257 (86.5)	267 (86.1)	1.03 [0.65; 1.64]
Operative vaginal delivery	40 (13.5)	43 (13.9)	1.09 [0.69; 1.72]
Cesarean birth			
Scheduled cesarean birth	44 (52.4)	26 (34.2)	**0.57 [0.34; 0.94]**
Emergency cesarean birth	40 (47.6)	50 (65.8)	1.29 [0.83; 2.01]
Cesarean birth due to NR-FHR pattern	19 (22.6)	18 (23.7)	1.06 [0.51; 2.22]
Cesarean section with SGA birth	2 (2.4)	12 (15.8)	**7.69 [1.66; 35.58]**
Birthweight outcomes			
Birthweight (g)	3300 (3056–3555)	3285 (2952–3572)	0.99 [0.98; 1.00]
Birthweight centile	50.4 (30.0–73.1)	49.7 (26.3–73.1)	0.99 [0.98; 1.01]
SGA <10 centile	28 (7.1)	46 (11.7)	**1.74 [1.06; 2.84]**
SGA <3 centile	4 (1.0)	9 (2.3)	2.29 [0.70; 7.50]
Neonatal outcomes			
Apgar score 1' <7	10 (2.5)	7 (1.8)	0.70 [0.26; 1.85]
Apgar score 5' <7	1 (0.2)	0	1.000
Admission at neonatal ICU	15 (3.8)	4 (1.0)	**0.27 [0.09; 0.80]**
Hypoxemia	1 (0.2)	1 (0.2)	1.01 [0.06; 16.13]
Neonatal death	1 (0.2)	0	1.000

Data provided as median (IQR) or number (%) with differences reported as odds ratios (OR) with 95% confidence intervals (95% CI) or *P* value (Fisher's exact test). Bold values indicate *P* value < 0.5.
CI, confidence interval; *ICU*, intensive care unit; *NR-FHR,* non-reassuring fetal heart rate; *OR*, odds ratio; *SGA*, small for gestational age.

RCT comparing the effectiveness of early vs late third trimester ultrasound.[7–11,25] The vast majority of fetal growth disorders in low-risk pregnancy occur at late gestations and it is therefore not surprising that SGA fetuses are frequently missed by an early third trimester scan.[1,2,5] Consistent with this hypothesis, the robust regression analysis indicated that in a low-risk population, the 28 to 32–week scan systematically overestimated BW at lower EFW centiles and underestimated it at higher EFW centiles. In contrast at 35 to 37 weeks, there was no fixed bias, confirming that the ultrasound performed at 35 to 37 weeks is more accurate in predicting BW centile than the assessment performed at 28 to 32 weeks.

Detection rates for small for gestational age detection

The detection rate of SGA at birth in the intervention arm was 20% which is lower than reported in previous studies of late third trimester scans with SGA diagnosis rates as high as 57%.[9–11,26] However, there is notable difference between the latter single-center trials with dedicated research staff vs pragmatic multicenter clinical studies done in a routine setting reporting lower SGA detection rates around 20% to 30% like in the present study.[7,8,27,28] A factor that may have contributed to dissimilar detection rates of SGA at birth in various studies is the nature and type of the antenatal fetal ultrasound growth reference or standard used to calculate EFW centiles[29,30] accounting for important differences in the proportion of fetuses antenatally labeled as SGA. In this study, Alter et al used different reference standards in the same population and demonstrated that the World Health Organization criteria identified 16.9% fetuses as SGA, significantly more than compared to only 5.2% using the IG21st standard.[31] In the POP study,[10] both ultrasound scans demonstrated higher sensitivity: this may be attributable to the fact that participants were recruited in UK centers and fetal size was assessed using the Hadlock (1985) growth charts, which were developed from an American cohort with limited ethnic diversity. Consequently, these charts may have provided a better "intrinsic fit" to the POP study population than the IG21st charts do to our cohort. The RELAIS trial used the IG21st charts as one of only a few available prescriptive fetal growth reference standards which map to both fetal EFW and neonatal BW. One possible explanation for the low sensitivity observed in our study lies in the calibration mismatch between the IG21st growth standards and our study population.[32] As shown in the Supplemental Figure 2, the distribution of EFW in our cohort is notably shifted above the IG21st curves, suggesting a systematic underestimation of fetal size when applying these standards. This discrepancy may have led to a failure in correctly classifying fetuses as SGA, particularly in the earlier scan, where measurement errors are more impactful and EFW is subject to greater measurement error, potentially leading to substantial variability—up to ±50% according to published data.[30] At the same time, the relatively modest sensitivity at 35 to 37 weeks and the very low false positive rates observed in both groups likely reflect a combination of population-related and methodological factors. The INTERGROWTH-21 standards are conservative and fetal weight distributions are shifted to the right, resulting in fewer fetuses falling below the 10th centile and a narrower detection window.

However, regardless of the presumed underestimation of SGA birth, the impact of the 35 to 37—week scan intervention on improving SGA detection and reducing NICU admissions without affecting either induction of labor or overall cesarean birth is evident. In fact, SGA detection confers clinical benefits in the intervention arm by significantly reducing NICU admission rates.

Obstetric interventions and perinatal outcomes

The justifications used in many national and international guidelines against the introduction of a universal late third trimester scan in pregnancy is concern over true/false positive SGA diagnosis leading to subsequent induction of labor, iatrogenic early term birth, and cesarean birth.[7,8,15,16] The prespecified secondary outcomes of the study confirm that the addition of a 35 to 37—week scan to routine care reduces NICU admission 3-fold without affecting induction of labor, cesarean section rates, or adverse neonatal outcomes. Among neonates admitted to NICU, most were delivered after emergency rather than scheduled cesareans. In the control arm, the cesarean births followed acute intrapartum events (nonreassuring FHR, bradycardia, cord prolapse), whereas in the intervention arm only one emergency cesarean occurred, for labor arrest.

Notably, the numerical difference in scheduled cesarean sections reflects planned obstetric indications unrelated to fetal compromise, such as low-lying placenta, maternal request, and breech presentation, while emergency cesarean sections in the control group were both more frequent and clinically more severe, consistent with a higher rate of acute intrapartum distress (nonreassuring fetal heart rate, bradycardia). We speculate that the additional late-third-trimester scan may have facilitated earlier recognition or management of late-onset complications, leading to timely and improved care provision mitigating adverse outcome reducing unplanned emergencies and subsequent NICU admissions.

This hypothesis is supported by the finding of a significant 8-fold increase in intrapartum cesarean birth of SGA pregnancies, reducing the likelihood that SGA fetuses were subject to intrapartum compromise. However, these findings must be interpreted with caution as the study was not powered for the secondary outcomes. The IUGR Risk Selection (IRIS) study trial of routine ultrasonography in the early and mid-third trimester vs routine clinical management demonstrated higher antenatal detection of SGA fetuses and increased induction of labor, without concomitant reduction in adverse perinatal outcomes.[27] Apart from the statistical limitations of the latter stepped wedge cluster RCT, the study also demonstrated a consistently low sensitivity (<15%) for SGA with both early and mid-third trimester ultrasound. Similar findings in another trial of mid-third trimester ultrasound[33] would suggest that the improvements in obstetrics outcomes seen in the current trial may be related to the late-third trimester scheduling of the ultrasound or a standardized approach to management for SGA diagnosis.

Implications for research

No formal cost-effectiveness evaluation was conducted in this study but future research will include such economic analyses. Moreover, with subsequent wider implementation of the late third trimester scan, it may be possible to consider undertaking larger studies to evaluate rarer adverse events such as neonatal hypoxic ischemic encephalopathy and perinatal mortality and longer-term infant and child outcomes. An emerging research area in this field is the newer concept of the distinction between SGA defined by a biometric standard of the SGA <10th centile reflecting impaired nutrition vs fetal growth restriction where the recent Delphi consensus criteria currently recommended by International specialist societies, which take into consideration growth velocity as well as Doppler ultrasound markers of placental dysfunction and fetal hypoxemia.[1,13,34,35] The potential for the use of Doppler ultrasound to improve perinatal outcome was demonstrated in a recent RCT that evaluated the effect of Doppler cerebroplacental ratio (CPR) in conjunction with ultrasound growth assessment on perinatal mortality and severe neonatal morbidity.[35] Rial-Crestelo et al showed a 40% reduction in both severe non-neurological morbidity and overall severe morbidity in the group where CPR was revealed.[35] Future studies will have to evaluate the additional effect of Doppler CPR evaluation in improving maternal and perinatal outcomes.

Implications for health policy

The RELAIS trial suggests that the implementation of a universal late third trimester scan would be expected to improve SGA detection and confer significant benefits by reducing NICU admission rates without increasing unnecessary interventions such as induction of labor, early preterm birth, or overall cesarean birth. Based on these results, health policy makers may consider that the policy of universal screening for fetal growth disorders at 35 to 37 weeks should be implemented at the expense of routine abdominal palpation, symphysis-fundal height measurement, and early third trimester scan assessment. Although health policy is often decided in a one test-one outcome framework, it would be important to consider the proven benefits of a late third trimester ultrasound in the detection of breech presentation, large-for-gestational-age fetuses, and fetal anomalies.[36] These additional complications that are relatively rare in isolation cumulatively affect about 1:20 pregnancies and have significant implications for subsequent pregnancy management and outcomes.

Conclusion

In this multicenter randomized trial conducted in low-risk pregnancies, the addition of a universal 35 to 37—week ultrasound assessment improved the detection of SGA at birth and reduces NICU admission rates without influencing early term birth, induction of labor, or overall cesarean section rates.■

Acknowledgments

Tina Pasciuto Research Core Facility Data Collection, Gemelli Science and Technology Park (GSTeP), Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

References

1. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333–9.

2. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.

3. Chauhan SP, Rice MM, Grobman WA, et al. Neonatal morbidity of small-and large for gestational age neonates born at term in uncomplicated pregnancies. Obstet Gynecol 2017;130:511–9.

4. Mendez-Figueroa H, Truong VT, Pedroza C, Khan AM, Chauhan SP. Small-for-gestational-age infants among uncomplicated pregnancies at term: a secondary analysis of 9 maternal-fetal medicine units network studies. Am J Obstet Gynecol 2016;215:628.e1–7.

5. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol 2018;218:S790–802.e1.

6. Trudell AS, Cahill AG, Tuuli MG, Macones GA, Odibo AO. Risk of stillbirth after 37 weeks in pregnancies complicated by small-for-gestational-age fetuses. Am J Obstet Gynecol 2013;208:376.

7. Monier I, Blondel B, Ego A, Kaminiski M, Goffinet F, Zeitlin J. Poor effectiveness of antenatal detection of fetal growth restriction and consequences for obstetric management and neonatal outcomes: a French national study. BJOG 2015;122:518–27.

8. Callec R, Lamy C, Perdriolle-Galet E, Patte C, Heude B, Morel O; EDEN Mother-Child Cohort Study Group. Impact on obstetric outcome of third-trimester screening for small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2015;46:216–20.

9. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 vs 32 weeks' gestation: a randomized trial (ROUTE). Ultrasound Obstet Gynecol 2015;46:391–7.

10. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the pregnancy outcome prediction (POP) study: a prospective cohort study. Lancet 2015;386:2089–97.

11. Caradeux J, Martinez-Portilla RJ, Peguero A, Sotiriadis A, Figueras F. Diagnostic performance of third-trimester ultrasound for the prediction of late-onset fetal growth restriction: a systematic review and meta-analysis. Am J Obstet Gynecol 2019;220:449–59.

12. ACOG practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 2013;121:1122–33. https://doi.org/10.1097/01.AOG.0000429658.85846.f9.

13. Morris RK, Johnstone E, Lees C, Morton V, Smith G; Royal College of Obstetricians and Gynaecologists. Investigation and care of a small-for-gestational-age fetus and a growth restricted fetus (Green-top guideline no. 31). BJOG 2024;131:e31–80. https://doi.org/10.1111/1471-0528.17814.

14. Khalil A, Sotiriadis A, D'Antonio F, et al. ISUOG practice guidelines: performance of third-trimester obstetric ultrasound scan. Ultrasound Obstet Gynecol 2024;63:131–47.

15. Fratelli N, Valcamonico A, Prefumo F, Pagani G, Guarneru T, Frusca T. Effects of antenatal recognition and follow-up on perinatal outcomes in small-for-gestational age infants delivered after 36 weeks. Acta Obstet Gynecol Scand 2013;92:223–9.

16. Winsloe C, Elhindi J, Vieira MC, et al. On behalf of the DESiGN trial team. Perinatal outcomes after selective third-trimester ultrasound screening for small-for-gestational age: prospective cohort study nested within DESiGN randomized controlled trial. Ultrasound Obstet Gynecol 2025;65:30–8. https://doi.org/10.1002/uog.29130.

17. NICE. Guideline development methods: information for national collaborating centres and guideline developers. London: National Institute for Health and Care Excellence; 2004.

18. Harris PA, Taylor R, Minor BL, et al. REDCap consortium, the REDCap consortium: building an international community of software partners. J Biomed Inform 2019;95:103208.

19. Salomon LJ, Alfirevic Z, Da Silva Costa F, et al. ISUOG practice guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol 2019;53:715–23.

20. Bhide A, Acharya G, Baschat A, et al. ISUOG practice guidelines (updated): use of doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol 2021;58:331–9.

21. Papageorgiou AT, O Ohuma E, Altman DG, et al. International standards for fetal growth based on serial ultrasound measurements: the fetal growth longitudinal study of the INTERGROWTH-21st project. Lancet 2014;384:869–79.

22. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. Lancet 2014;384:857–68.

23. Fleiss JL. Statistical method or rates and proportions, II Ed. New York: John Wiley & Sons; 1981. p.45.

24. Lees CC, Stampalija T, Baschat A, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020;56:298–312. https://doi.org/10.1002/uog.22134.

25. Mustafa HJ, Javinani A, Muralid-haran V, et al. Diagnostic performance of 32 vs 36 weeks ultrasound in predicting late-onset fetal growth restriction and small-for-gestational-age neonates: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2024;6:101246.

26. Wanyonyi SZ, Orwa J, Ozelle H, et al. Routine third-trimester ultrasound for the detection of small-for-gestational age in low-risk pregnancies (ROTTUS study): randomized controlled trial. Ultrasound Obstet Gynecol 2021;57:910–6.

27. Henrichs J, Verfaille V, Jellema P, et al. Effectiveness of routine third trimester ultrasonography to reduce adverse perinatal outcomes in low risk pregnancy (the IRIS study): Nationwide, pragmatic, multicentre, stepped wedge cluster randomised trial. BMJ 2019;367:l5517.

28. Verspyck E, Thill C, Ego A, et al. Screening for small for gestational age infants in early vs late third-trimester ultrasonography: a randomized trial. Am J Obstet Gynecol MFM 2023;5:101162.

29. Mascherpa M, Pegoire C, Meroni A, et al. Prenatal prediction of adverse outcome using different charts and definitions of fetal growth restriction. Ultrasound Obstet Gynecol 2024;63:605–12.

30. Dudley NJ. The management of error in ultrasound fetal growth monitoring. Ultrasound 2021;29:4–9. https://doi.org/10.1177/1742271X20945749.

31. Alter R, Cohen A, Kremer E, Ormianer M, Ezra Y, Kabiri D. Comparison of SGA and severe SGA rates using six size standards - is there a difference? Eur J Obstet Gynecol Reprod Biol 2024;301:234–9. https://doi.org/10.1016/j.ejogrb.2024.08.008.

32. Stampalija T, Ghi T, Rosolen V, et al. SIEOG working group on fetal biometric charts. Current use and performance of the different fetal growth charts in the Italian population. Eur J Obstet Gynecol Reprod Biol 2020;252:323–9. https://doi.org/10.1016/j.ejogrb.2020.06.059.

33. Skråstad RB, Eik-Nes SH, Sviggum O, et al. A randomized controlled trial of third-trimester routine ultrasound in a non-selected population. Acta Obstet Gynecol Scand 2013;92:1353–60.

34. Stampalija T, Wolf H, Mylrea-Foley B, et al. TRUFFLE-2 feasibility study authors. Reduced fetal growth velocity and weight loss are associated with adverse perinatal outcome in fetuses at risk of growth restriction. Am J Obstet Gynecol 2023;228:71.e1–10. https://doi.org/10.1016/j.ajog.2022.06.023.

35. Rial-Crestelo M, Lubusky M, Parra-Cordero M, et al. Term planned delivery based on fetal growth assessment with or without the cerebroplacental ratio in low-risk pregnancies (RATIO37): an international, multicentre, open-label, randomised controlled trial. Lancet 2024;403:545–53.

36. Fitiri M, Papavasileiou D, Mesaric V, Syngelaki A, Akolekar R, Nicolaides KH. Routine 36-week scan: diagnosis and outcome of abnormal fetal presentation. Ultrasound Obstet Gynecol 2025;65:154–62.

Author and article information

From the Department of Women and Child Health, Women Health Area, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Università Cattolica del S. Cuore, Rome, Italy (Alessandra, Giulia M, Giulia FM, Elisa, Giovanni and Tullio); Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy (Tamara); Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy (Tamara); Obstetrics and Gynecology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy (Federico); Clinical Epidemiology and public Health research Unit Institute for maternal and child Health — IRCCS Burlo Garofolo, Trieste, Italy (Giulia Z and Lorenzo); Department of Obstetrics and Gynecology, Casilino General Hospital, Rome, Italy (Grazia); Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy (Herbert); Department of Obstetrics and Gynecology, Casilino General Hospital, Rome, Italy (Herbert); Department of Woman, Child and General and Specialised Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy (Maddalena); Department of Neurosciences Reproductive Science and Dentistry, University Federico II, Naples, Italy (Laura); Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy (Daniele and Giuseppe); Department of Obstetrics and Gynecology Ospedale Cristo Re Roma, Rome, Italy (Ilenia); Department of Woman's and Child's Health, University of Padova, Padova, Italy (Silvia); Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy (Anna); Department of Woman, Child and Neonate, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (Tatjana and Enrico); and Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK (Baskaran).

F.A. and S.T. Joint first authors.

G.T. and F.E. Joint last authors.

Received Aug. 30, 2025; revised Nov. 18, 2025; accepted Nov. 18, 2025.

The study is registered at ClinicalTrials.gov (NCT05787054) https://clinicaltrials.gov/study/NCT05787054 on the first of March, 2023. The date of initial participant enrollment was in January 2021.

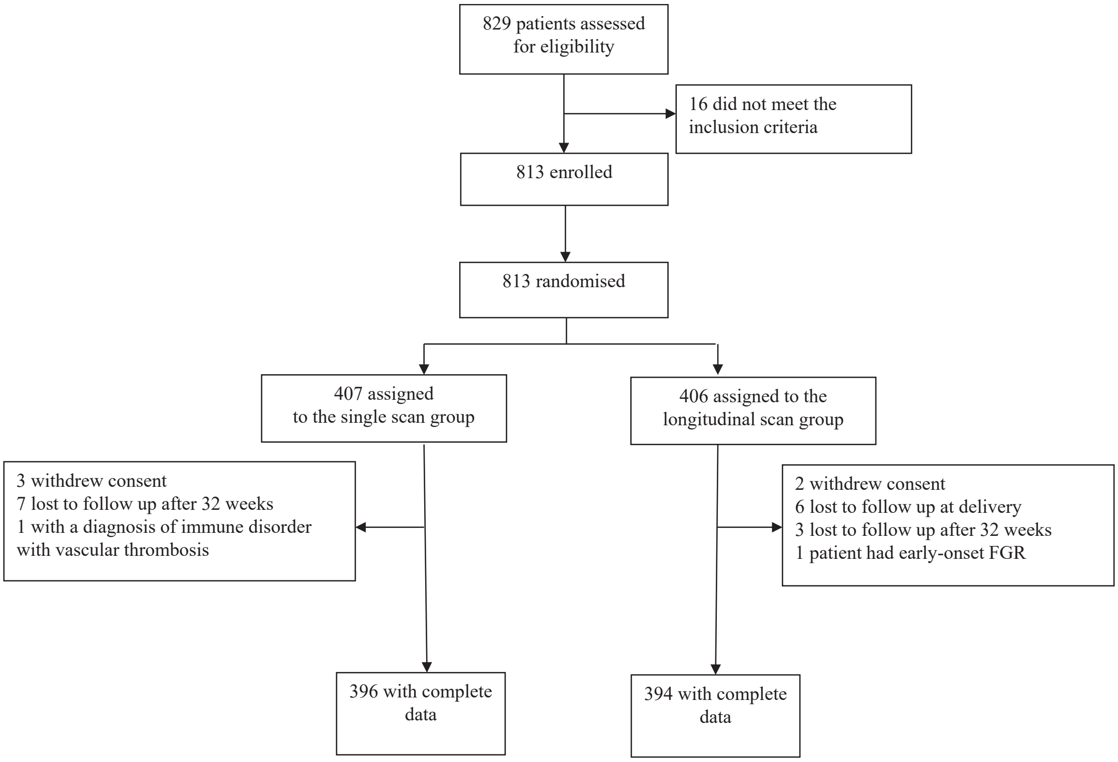
The authors report no conflict of interest.

This research was funded by Italian Society of Obstetrics and Gynecology (SIGO).

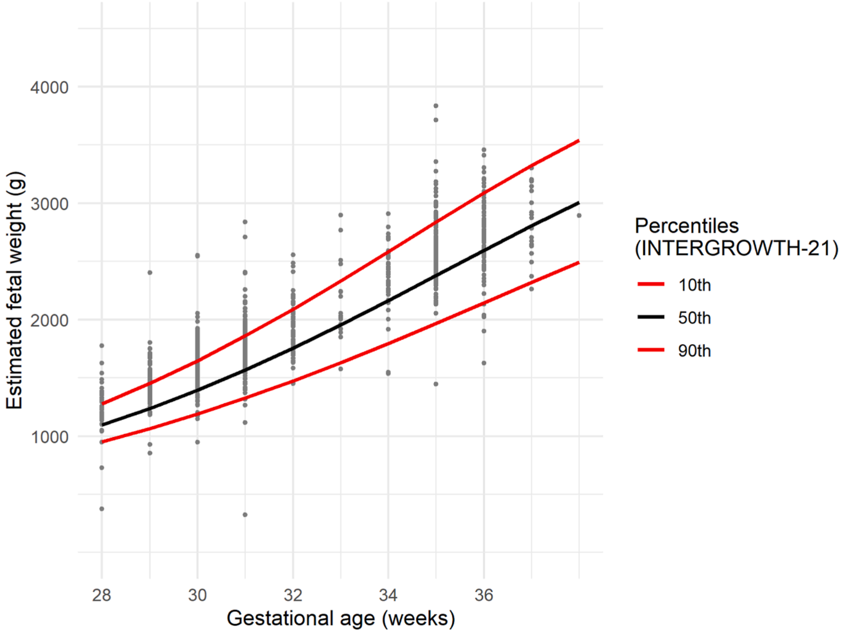
Anonymized individual participant data, the study protocol, statistical analysis plan, and informed consent form will be available after publication via e-mail after approval of a proposal with a signed data access agreement.

Corresponding author: Alessandra Familiari. alessandra.familiari@policlinicogemelli.it

SUPPLEMENTAL FIGURE 1
Trial profile. CONSORT flow diagram



SUPPLEMENTAL FIGURE 2
EFW plotted against GA (weeks) according to Intergrowth-21st standard



EFW, estimated fetal weight.

SUPPLEMENTAL TABLE 1
Recruiting centers and contribution of each center to the study population

Centers	Total N=790, n (%)	Single scan N=396, n (%)	Longitudinal scan N=394, n (%)
Brescia, Spedali Civili	52 (6.6)	26 (6.6)	26 (6.6)
Milan, Mangiagalli	147 (18.6)	71 (17.9)	76 (19.3)
Naples, Federico II	80 (10.1)	44 (11.1)	36 (9.1)
Naples, Vanvitelli	20 (2.5)	10 (2.5)	10 (2.5)
Rome, Cristo Re	22 (2.8)	11 (2.8)	11 (2.8)
Rome, Policlinico Umberto I	11 (1.4)	6 (1.5)	5 (1.3)
Rome, Policlinico Casilino	62 (7.9)	29 (7.3)	33 (8.4)
Rome, Policlinico A, Gemelli	142 (18.0)	74 (18.7)	68 (17.3)
Bari, Policlinico	36 (4.6)	17 (4.3)	19 (4.8)
Padova, Università Ospedaliera	114 (14.4)	58 (14.7)	56 (14.2)
Trieste, IRCCS Burlo Garofolo	104 (13.2)	50 (12.6)	54 (13.7)