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Abstract

Introduction:

The aim of this study was to evaluate the ac- curacy of 35–37 weeks' ultrasound for fetal growth restriction (FGR) detection and the impact of 30th–33rd weeks versus 30th–33rd and 35th–37th weeks' ultrasound on perinatal outcomes.

Methods:

This was a randomized controlled trial that enrolled 1,061 low-risk pregnant women: 513 in the control group (routine ultrasound performed at 30th–33rd weeks) and 548 in the study group (with an additional ultrasound at 35th–37th weeks). FGR was defined as a fetus with an estimated fetal weight (EFW) below the 10th percentile. p values < 0.05 were considered statistically significant.

Results:

The ultrasound at 35–37 weeks had an overall accuracy of FGR screening of 94%. Spearman's correlation coefficient between EFW and birthweight centile was higher for at 35–37 weeks' ultrasound (ρ = 0.75) compared with 30–33 weeks' ultrasound (ρ = 0.44). The study group had a lower rate of operative vaginal deliveries (24.4% vs. 39.3%, p = 0.005) and caesarean deliveries for non-reassuring fetal status (16.8% vs. 38.8%, p < 0.001).

Discussion/Conclusion:

A later ultrasound (35–37 weeks) had a high accuracy for detection of FGR and had a higher correlation between EFW and birth- weight centiles. Furthermore, it was also associated with lower adverse perinatal outcomes compared to an earlier ultrasound.

Introduction

Sonographic estimation of fetal weight (EFW) during the third trimester in low-risk pregnancy is considered the most effective method for diagnosis of fetal growth restriction (FGR) [1]. However, there is no consensus on the need for a routine third trimester ultra- sound and the best gestational age to perform it [2]. The main argument against a routine third trimester ultra- sound is the possibility of overdiagnosis and unnecessary obstetric intervention for FGR since a significant proportion of these fetuses are constitutively small for gestational age (SGA). On the other hand, undiagnosed late FGR

constitutes a significant proportion of term stillbirths [3, 4] and is associated with higher risk of adverse neonatal outcomes when compared to FGR diagnosed during pregnancy [5, 6]. Despite this, it is routinely used in many countries during early third trimester, a strategy that has been endorsed by the World Health Organization (WHO) [7].

In accordance with recent guidelines from the Inter- national Society of Ultrasound in Obstetrics and Gynecology (ISUOG), screening for FGR is an essential com- ponent of antenatal care and fetal ultrasound plays a key role in assessment of this condition [8]. It is important to differentiate between the concept of fetal size at a given time point and fetal growth, the latter being a dynamic process, which requires at least two scans separated in time. In Portugal, according to local guidelines of Direcção Geral de Saúde (DGS) from 2015, FGR screening in low-risk pregnancies is performed with an ultrasound for EFW at 30th–33rd weeks [9]. Nonetheless, data from ROUTE study, which was a randomized trial, showed that FGR detection rate was superior at 36 versus 32 weeks' gestation [10]. The aim of this study was to evaluate the accuracy of an additional 35th–37th weeks' ultrasound for late FGR detection and the impact on perinatal outcomes.

Materials and Methods

A prospective randomized trial was conducted to compare the accuracy of ultrasound screening for late FGR between 30th–33rd weeks and 35th–37th weeks. The study was approved by the Lisbon Academic Medical Center Ethics Committee (reference number 387/13). This work was supported by a Research Grant from Fundação para a Ciência e Tecnologia (FCT)-SFRH/ SINTD/92997/2013. The funder was not involved in the study design, collection, analysis, data interpretation, or in the writing of this report. The trial was registered in ClinicalTrials.gov with the identification number: NCT03200665.

The population included in this study corresponded to low-risk pregnant women referred by the Primary Care units to Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, in accordance with local guidelines. According to national guide- lines, routine ultrasound scans were performed at 11 + 0 to 13 + 6 weeks' gestation for pregnancy dating, based on crown rump length; screening for congenital anomalies was performed at 20 + 0 to 22 + 6 weeks' gestation and screening of abnormal fetal growth at 30 + 0 to 32 + 6 weeks' gestation.

All women included in the study had a 30–33 weeks' ultrasound according to national protocols. After routine third trimester scanning, women meeting the following inclusion criteria were eligible to participate in the study: (1) viable singleton non-anomalous fetus; (2) pregnancy dating by ultrasound performed before 13 + 6 weeks; (3) maternal age at recruitment ≥18 years; and (4) the absence of medical history of diabetes, autoimmune or renal diseases, anemia, hypertension, FGR, or stillbirth.

Patients who agreed to participate in the study, after signing an informed consent, were randomized into two groups (with and without an additional scan at 35th–37th weeks). Randomization was done through computer software, and sequences were generated in blocks of 100 participants to assure balanced distribution within study arms, in a 1:1 allocation ratio. Once a patient consented to enter the trial, a sealed opaque envelope was opened, and the patient was then allocated to the study or control group. It was not possible to blind participants, obstetricians, or outcome assessors to the trial groups.

Clinical data were collected at the time of enrolment such as maternal age, ethnicity, parity, height, weight, and body mass index at the beginning of pregnancy, education, and smoking habits. Clinical evaluation included measurement of symphysis-fundus distance (SFD).

Obstetric and neonatal outcomes were registered prospectively after delivery by revising medical records such as gestational age at delivery, type of labor, type of delivery, indication for operative vaginal or cesarean delivery, cardiotocographic (CTG) register characteristics, gender, birthweight, birthweight centile, evidence of meconium staining of amniotic fluid, Apgar score, admission to neonatal intensive care unit, and perinatal mortality.

The primary outcome was to evaluate the accuracy of 35–37 weeks' ultrasound for FGR detection and compare the correlation of 35–37 weeks' EFW centile with birthweight centile with the correlation of EFW centile at 30–33 weeks' ultrasound with birth- weight centile. Secondary outcomes were to compare perinatal data between study and control groups.

The ultrasound performed for the study group included bio- metric parameters of the fetus: biparietal diameter, head circumference (HC), abdominal circumference (AC), and femur length.

All were obtained at the appropriate levels described elsewhere, with the fetal structure of interest filling at least 30% of the monitor [11, 12]. BDP and HC were taken from axial images of the fetal brain at the transthalamic plane, with an angle of insonation as close as possible to 90°. Particularly in late gestation, this section plane is easier to identify and allows more reproducible measurements than does the transventricular plane [13]. The midline echo (representing the falx cerebri) had to be broken anteriorly, at a third of its length, by the cavum septum pellucidum. Biparietal diameter was measured by outer-to-inner caliper placement at the widest part of the skull. We adopted outer-to-inner technique in order to avoid artefacts generated by the distal echo of the calvarium. AC measurement was taken in a cross-sectional view of the fetal abdomen as close as possible to circular, at the level of the bifurcation of the main portal vein into left and right branches and with the stomach visible. Both HC and AC were measured using the ellipse facility on the outer border of the skull and of the abdomen, respectively. Femur length was measured using a longitudinal view of the fetal thigh closest to the probe and with the femur as close as possible to the horizontal plane. Measurement was performed with the full length of the bone visualized by including only the femoral diaphysis length, excluding the hypoechogenic cartilaginous structures at either end of the femur. Based on these four measurements, the computer system (Astraia®) provided the EFW and respective percentile according to the Hadlock formula [14] and Yudkin curves [15]. Amniotic fluid was measured by single pocket depth. Functional evaluation included Doppler of the umbilical artery (UA), middle cerebral artery, and uterine artery. The respective pulsatility index and cerebroplacental ratio were registered. FGR was defined according to the American College of Obstetricians and Gynecologists (ACOG) as a fetus with an EFW be- low the 10th percentile and SGA as a newborn with a birthweight below the 10th percentile [16].

For the control group, local guidelines for follow-up were followed with serial evaluation of the SFD at the scheduled appointments at 35, 38, 40, and 41 weeks. If this distance was less than 31 cm at 35 weeks or less than 34 cm at 38, 40, and 41 weeks, the clinical suspicion of FGR mandated an ultrasound evaluation as described above. If no deviation of SFD was found, induction of labor was scheduled after 41 weeks, and delivery route was decided by obstetric criteria.

In accordance with our department's protocol for surveillance of FGR, the management follow-up was as described below:

- FGR with EFW <10th centile and normal Doppler: Doppler re-evaluation after 1 week of diagnosis and EFW + Doppler after 2 weeks. If Doppler is normal and the fetus remains on the same growth curve, ultrasound controls are performed every 2 weeks and delivery is scheduled at 39th week.
- FGR with EFW or AC < 3rd centile or EFW <10th centile + UA IP >95th centile: weekly Doppler and CTG. EFW every 2 weeks. If Doppler is normal in all evaluations, delivery is scheduled at 37th week.
- FGR with cerebroplacental ratio <5th centile or middle cerebral artery pulsatility index < 5th centile: Doppler evaluation three times per week; CTG every 8 h; and EFW every 2 weeks. If no additional Doppler anomalies in all evaluations, delivery is scheduled at 37th week.
- FGR with absent or reversed end diastolic flow in UA is an indication for delivery at the gestational age of the ultrasound evaluation in the study group.

For all groups, in case of Doppler anomalies, they were con- firmed within 6–12 h. Delivery route was decided according to obstetric criteria. For both groups, confirmation of antenatal detection of FGR was assessed after the baby was born, by comparing antenatal EFW centiles of both ultrasounds with birthweight percentiles. Nonreassuring fetal status was defined by the interpretation of continuous CTG, using the American College of Obstetricians and Gynecologists classification [17].

Normal distributions were assessed using the Kolmogorov- Smirnov test. Data are presented as mean ± standard deviation, median (interquartile range), or number of subjects (%). Statistical analyses were performed using Stata 14.1 (Statacorp, College Station, TX, US) and R-3.3.2.

$\chi 2$ tests or Fisher's exact tests and Student's t test or Mann-Whitney U test were used to compare categorical and continuous variables between groups, respectively. Spearman's correlation coefficient was used to test the correlation between EFW centile and birthweight centile.

According to our retrospective data, the antenatal detection rate of FGR at 30–33 weeks' ultrasound was 20.5% for low-risk pregnancies [18]. Aiming to increase the detection rate by at least 7% with an ultrasound at 35th–37th weeks (study group), the investigators would require a total sample of 1,200 women (600 in each group – control with ultrasound at 30–33 weeks and study with an additional ultrasound at 35–37 weeks), with 80% power and a significance α level of 0.05. Analysis was based on originally assigned groups (intention-to-treat). A secondary per-protocol analysis was performed by excluding the cases that missed the scheduled ultrasound from the study group and the cases that were submitted to an additional ultrasound after enrolment from the control group. For all comparisons, two-sided p values < 0.05 were considered statistically significant.

Results

Figure 1 shows a flowchart of the participants and the reasons for exclusion in both groups. Pregnant women were enrolled between July 2015 and May 2019. A total of 1,093 pregnant women were randomized to control (n = 535) and study (n = 558) groups. Of these women, 32 (2.9%) were lost to follow up (2 before the scan and 30 during the scan-to-delivery interval). Baseline characteristics of participants lost to follow up were comparable to the 1,061 who completed the study, except for a lower maternal age at randomization in the subset lost to follow up (Table 1). Demographic

characteristics did not differ between control (n = 513) and study (n = 548) groups (Table 2). Table 3 summarizes perinatal outcomes. A total of 98 (9.2%) newborns were found to be SGA (birth- weight <10th centile). Within the 52 cases of SGA in the study group, the ultrasound at 35–37 weeks' gestation detected 26 (50%). The study group had a lower rate of operative vaginal deliveries for nonreassuring fetal status (24.4% vs. 39.3%, p = 0.005) and a lower rate of cesarean deliveries for nonreassuring fetal status (16.8% vs. 38.8%, p < 0.001) (Table 3). No perinatal mortality was registered in any of the groups.

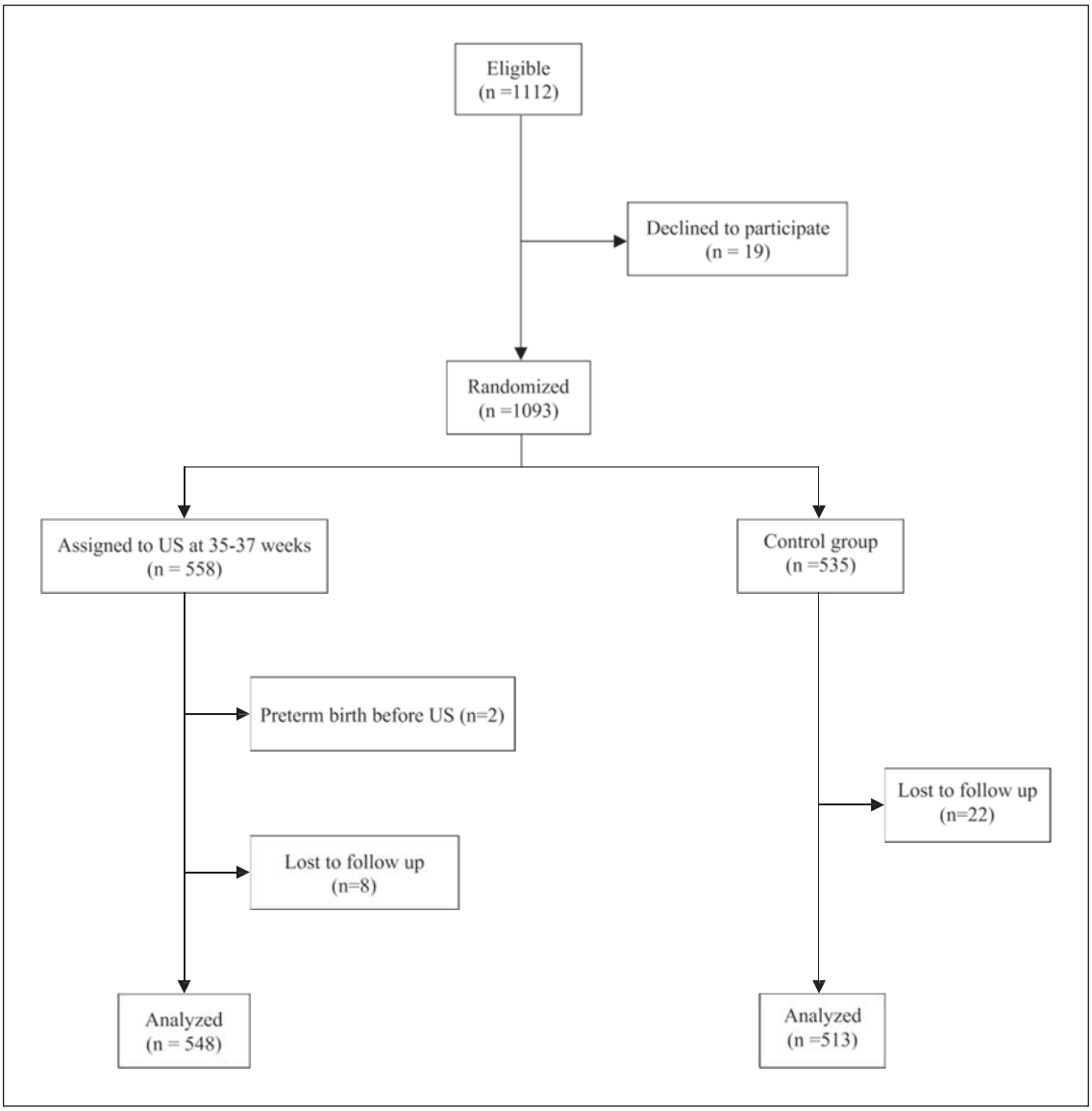

Fig. 1. Flowchart summarizing selection and grouping of study and control groups.

Per protocol, 501 out of 548 participants in the study group effectively underwent an additional scan at 35–37 weeks' gestation. Forty-seven (8.6%) participants did not attend the additional ultrasound that was scheduled. We tried to contact these patients by phone to reschedule the scan, but in 30 patients there was no date available to per- form the scan in the gestational age frame defined, and 17 patients did not answer the phone. In the control group, three women performed a scan for low SFD and all of these were excluded before per protocol analysis, resulting in a total of 510 control

patients. Baseline characteristics were comparable between groups (Table 4). The rate of SGA was similar between study and control groups (50/501 [10%] versus 45/510 [8.8%], p = 0.53). Similarly, to the intention-to-treat analysis, the study group had a lower rate of operative vaginal deliveries for nonreassuring fetal status (36/158 [22.8%] versus 52/134 [38.8%], p = 0.003) and a lower rate of cesarean deliveries for non- reassuring fetal status (16/101 [15.8%] versus 40/103 [38.8%], p < 0.001), compared to control group (Table 4). For the study group, 31 cases had a diagnosis of FGR at the 35–37 weeks' ultrasound. Comparing this group with the group with EFW ≥10th centile, the median gestation- al age at delivery was lower for the FGR group (39 [38–39.6] versus 40.1 [39.1–40.6], p < 0.001).

Table 1. Demographic characteristics of 1,093 pregnant women randomly assigned to undergo an additional ultrasound examination at 35–37 weeks' gestation versus 30–33 weeks' gestation ultrasound according to follow-up status

Variables	Completed (*n* = 1,061)	Lost (*n* = 32)	*p* value
Maternal age (median [IQR]), years	30 (26–34)	27.5 (25–31.5)	0.02
Maternal height (mean ± SD), m	1.63±0.06	1.64±0.06	0.50
Maternal weight at beginning of pregnancy (median [IQR]), kg	61 (55–70)	60 (56–70)	0.86
Body mass index at beginning of pregnancy (median[IQR]), kg/m^2	23 (20.7–26.2)	22.8 (20.9–25.3)	0.90
Increase in weight during pregnancy at randomization (median[IQR]), kg	11 (9–15)	10 (8–14)	0.65
Parity, *n* (%)			
Nulliparous	573 (54)	13 (41)	0.61
Multiparous	488 (46)	19 (59)	
Marital status, *n* (%)			
Single	295 (28.1)	14 (43.7)	0.08
Married	443 (42.2)	6 (18.8)	
Co-habitant	299 (28.4)	12 (37.5)	
Divorced	13 (1.2)	0 (0)	
Widowed	1 (0.1)	0 (0)	
Ethnicity, *n* (%)			
White	939 (88.5)	26 (81.2)	0.30
Black	116 (10.9)	6 (18.8)	
Mixt	2 (0.19)	0 (0)	
Asian	4 (0.38)	0 (0)	
Education, *n* (%)			
Doctoral level	7 (0.7)	0 (0)	0.06
Master level	44 (4.2)	0 (0)	
Degree level	337 (32)	8 (25)	
High school (12th grade)	337 (32)	11 (34.4)	
Middle school (9th grade)	256 (24.3)	6 (18.7)	
Elementary school (4th grade)	62 (5.9)	7 (21.9)	
Less than elementary school	10 (0.9)	0 (0)	
Smoker at randomization, *n* (%)	164 (15.5)	6 (18.8)	0.61

IQR, interquartile range; SD, standard deviation.

Considering only the pregnant women that performed ultrasound at 35–37 weeks' gestation in the study group (n = 501), this exam detected correctly 52% (26/50) of cases of SGA that had been missed by the standard 30–33 weeks' gestation ultrasound and also correctly considered appropriate weight for gestational age 446 cases (EFW ≥10th percentile) that corresponded to newborns with ap- propriate weight for gestational age at delivery (birth- weight ≥10th percentile), with overall accuracy, i.e., (true positives + true negatives)/all observations of 94% (26 +446)/501.

Spearman's correlation coefficient was higher between the EFW centile at 35–37 weeks' ultrasound and birth-weight centile (ρ = 0.75) than the correlation coefficient between the EFW centile at 30–33 weeks' ultrasound and birthweight centile (ρ = 0.44). For prediction of SGA, area under the receiver-operating characteristics curve (AUC) of the estimated fetal-weight centile at 35–37 weeks' ultrasound was 0.90 (95% CI, 0.86–0.95) (Fig. 2).

Table. 2. Demographic characteristics of pregnant women randomly assigned to undergo an additional ultrasound examination at 35–37 weeks' gestation (study group) versus 30–33 weeks' gestation (control group)

Variables	Control group (n = 513)	Study group (n = 548)	p value
Maternal age (median [IQR]), years	30 (26–35)	30.5 (26–34)	0.93
Maternal height (mean ± SD), m	1.63±0.06	1.63±0.06	0.18
Maternal weight at beginning of pregnancy (median [IQR]), kg	61(55–70)	60 (54–70)	0–35
Body mass index at beginning of pregnancy (median [IQR]), kg/m^2	23.1 (21–26.3)	22.8 (20.6–26.1)	0.23
Increase in weight during pregnancy at randomization (median [IQR]), kg	11 (9–14)	11 (9–15)	0.67
Parity, n (%)			
Nulliparous	269 (52.4)	304 (55.5)	0.32
Multiparous	244 (47.6)	244 (44.5)	
Marital status, n (%)			
Single	138 (27.2)	157 (28.9)	0.85
Married	212 (41.8)	231 (42.4)	
Co-habitant	149 (29.4)	150 (27.6)	
Divorced	7 (1.4)	6 (1.1)	
Widowed	1 (0.2)	0 (0)	
Ethnicity, n (%)			
White	457 (89)	482 (88)	0.42
Black	55 (11)	61 (11)	
Mixt	0 (0)	2 (0.36)	
Asian	1 (0.19)	3 (0.55)	
Education, n (%)			
Doctoral level	4 (0.8)	3 (0.6)	0.70
Master level	24 (4.7)	20 (3.7)	
Degree level	153 (30.1)	184 (33.8)	
High school (12th grade)	175 (34.5)	162 (29.7)	
Middle school (9th grade)	126 (24.8)	130 (23.8)	
Elementary school (4th grade)	21 (4.1)	41 (7.5)	
Less than elementary school	5 (1.0)	5 (0.9)	
Smoker at randomization, n (%)	79 (15.4)	85 (15.5)	0.96

IQR, interquartile range; SD, standard deviation.

Table 3. Perinatal outcomes of pregnant women randomly assigned to undergo an additional ultrasound examination at 35–37 weeks' gestation (study group) versus 30–33 weeks' gestation (control group)

Variables	Control group (n = 513)	Study group (n = 548)	p value
Labor induction, n (%)	133 (25.9)	162 (29.6)	0.19
Gestational age at delivery (median [IQR]), weeks	40 (39–40.5)	40 (39.1–40.5)	0.83
Male gender, n (%)	266 (51.9)	284 (51.8)	0.99
Birthweight (median [IQR]), g	3,295 (3,030–3,615)	3,282.5 (3,035–3,620)	0.99
Birthweight centile (median [IQR])	39.6 (22.7–64.1)	39.2 (21.7–64.9)	0.64
Birthweight, n (%)			
<10th centile	46 (9.0)	52 (9.5)	0.77
<3rd centile	9 (1.8)	8 (1.5)	0.81
Operative vaginal delivery, n (%)	135 (26.3)	168 (30.7)	0.12
Operative vaginal delivery for nonreassuring fetal status, n (%)	53 (39.3)	41 (24.4)	0.005
Cesarean delivery, n (%)	103 (20)	107 (19.5)	0.82
Cesarean delivery for nonreassuring fetal status, n (%)	40 (38.8)	18 (16.8)	<0.001

Table 4. Comparison of baseline characteristics and perinatal outcomes of pregnant women randomly assigned to undergo an additional ultrasound examination at 35–37 weeks' gestation (study group) versus 30–33 weeks' gestation (control group) – per protocol

Baseline characteristics	*p* value	Perinatal outcomes	*p* value
Maternal age	0.72	Labor induction	0.10
Maternal height	0.08	Gestational age at delivery	0.22
Maternal weight at beginning of pregnancy	0.46	Male gender	0.73
Body mass index at beginning of pregnancy	0.29	Birthweight	0.82
Increase in weight during pregnancy at randomization	0.64	Birthweight centile	0.67
Parity	0.17	Birthweight	
		<10th centile	0.53
		<3rd centile	0.84
Marital status	0.69	Operative vaginal delivery	0.07
Ethnicity	0.60	Operative vaginal delivery for nonreassuring fetal status	0.003
Education	0.98	Cesarean delivery	0.99
Smoker at randomization	0.84	Cesarean delivery for nonreassuring fetal status	<0.001

Conclusion

This prospective randomized trial provided evidence that performing a routine third trimester ultrasound at 35–37 weeks' gestation had an overall accuracy of 94% for FGR detection and was associated with better perinatal outcomes. If we compare these data with our previous retrospective study [18] that included low-risk pregnancies with routine third trimester screening at 30–33 weeks' gestation [9], this earlier ultrasound had a lower overall accuracy of 89%.

Despite our small sample, we have only included low- risk pregnancies with no maternal risk factors, and we followed a specific protocol after diagnosis of FGR at 35–37 weeks' gestation ultrasound with well-defined follow- up scans and timing to schedule delivery. The lower gestational age at delivery for the group with EFW <10th centile at 35–37 weeks' gestation compared with EFW≥10th centile may reflect the different surveillance and management provided for the first group. Since national guidelines recommend 30–33 weeks' screening ultra- sound, we could not have avoided this scan in the study group, so we have only included patients that already had an appropriate EFW at 30–33 weeks. This strategy of se- rial scanning in the study group may have contributed to improve detection of FGR and perinatal outcomes such as the lower rate of cesarean and operative vaginal deliveries for nonreassuring fetal status. The detection rate of SGA of 52% (26/50) in the study group was comparable to the recent ROTTUS that has demonstrated a detection rate of SGA infants by routine third trimester ultrasound at 36 + 0 to 37+6 weeks of 52.8% (19/36) [19].

A limitation of our study was slow recruitment, which led us to stop the trial when we had more than 90% of the planned sample. We consider that this decision does not affect the conclusions of our trial since we found significant differences of accuracy between 30 and 33 weeks' and 35–37 weeks' gestation ultrasounds and important clinical and statistical differences in meaningful perinatal outcomes. Recruitment of patients in only one hospital has contributed to slow recruitment and may hamper generalization of the results but has also allowed us to have a very low rate of loss to follow-up (2.9%).

Clinicians and pregnant women were not blinded to the study group which may contribute at least partially to some work-up biases. The knowledge of a normal scan some weeks before labor may have contributed to a high- er threshold for the decision of an operative vaginal de- livery and for the diagnosis of nonreassuring fetal status.

In our series, the area under the receiver-operating characteristics curve of 90% reinforces that an ultrasound at 35th–37th weeks' has a good performance for screening of FGR. Previous studies have already demonstrated that FGR detection rate was superior at 36 versus 32 weeks' gestation [10] but without better perinatal out- comes [2, 10]. For one instance, meta-analysis has limited contemporary validity as they have used outdated surrogates of fetal growth or protocols in which FGR diagnosis elicited no change in management [2]. Furthermore, some studies have included pregnant women with maternal risk factors diagnosed after randomization which may have introduced a bias in the evaluation of perinatal out- comes [10]. Recently, the ROTTUS study has demonstrated that routine ultrasound performed between 36 + 0 and 37 + 6 weeks was superior to selective ultrasound based on serial symphysis-fundus height measurements for the detection of true SGA [19].

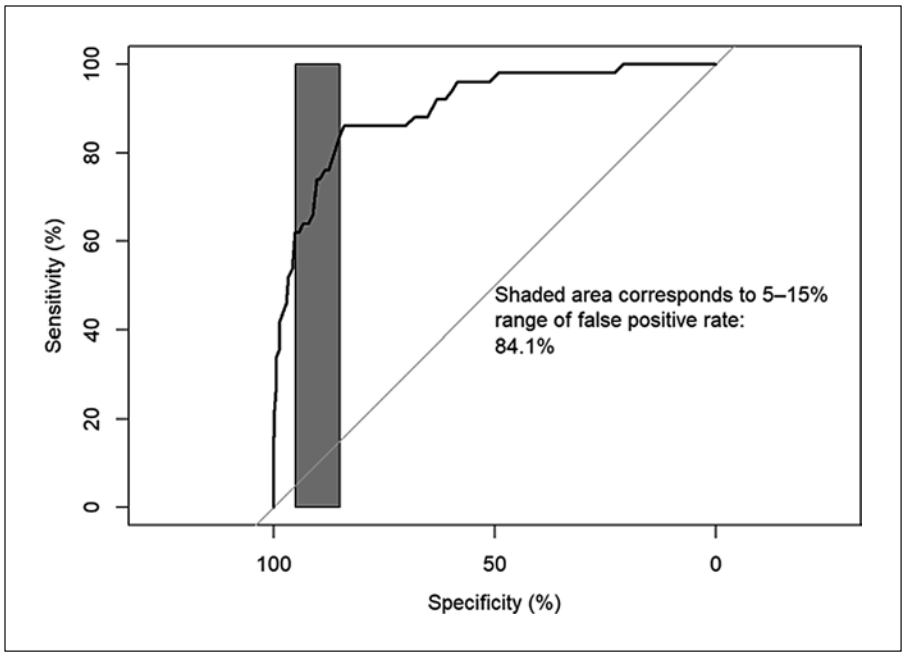

Fig. 2. Area under the receiver-operating characteristics curve for ultrasound performed at 35th–37th week's gestation for prediction of fetal growth restriction.

The higher correlation coefficient between EFW percentile at 35–37 weeks' ultrasound and birthweight centile when compared to 30–33 weeks' ultrasound is in accordance with other studies that concluded that the closer the delivery occurs to the assessment, the higher the predictive performance of the scan [20, 21]. Furthermore, a later scan during the third trimester may be more appropriate to identify fetuses that only begin to decelerate their growth after the scan at 30–33 weeks' gestation. One can argue that if we consider replacing the 30–33 weeks' ultrasound by a later scan, the delay in the diagnosis of FGR may contribute to adverse perinatal outcomes. Our study was underpowered to detect events with low prevalence such as perinatal mortality, but others have already demonstrated that fetal death is higher for FGR in the late term and post term periods than in the preterm period [22].

Some authors [23, 24], but not all [25, 26], have reported that reduced third trimester growth velocity is as- sociated with an increased incidence of certain adverse pregnancy outcomes. According to ISUOG guidelines and Delphi consensus, fetal growth analysis may help in the management of pregnancy [8,

27]. An additional ultrasound during the third trimester has constrains in terms of human and economic resources available to be feasible. However, we have also to consider the potential reduction of costs that will be possible by reducing obstetric intervention during delivery. This should be clarified in a future cost-effective study.

To conclude, in a country that recognizes the value of routine third trimester ultrasound screening of FGR for low-risk pregnancies, our data are important to reinforce that a later ultrasound during the third trimester has a high accuracy for detection of FGR and has a high correlation between EFW and birthweight centiles. Further- more, it may also contribute to diminish adverse perinatal outcomes compared to an earlier ultrasound during third trimester, which reinforces that antenatal identification of FGR allows close monitoring and appropriate management, preventing the need of emergent obstetric intervention during labor and delivery.

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Statement of Ethics

The study was approved by the Lisbon Academic Medical Center Ethics Committee (reference number 387/13). Written in- formed consent was obtained from all patients who agreed to participate in the study.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

Catarina Policiano had the idea for the study, designed the study, performed the ultrasounds and recruited patients, per- formed the statistical analysis, and wrote the first draft of the article. Nuno Clode had the idea for the study, designed the study, checked the analysis, and revised and co-wrote the article. Luis M. Graca designed the study, checked the analysis, and revised and co-wrote the article. Jorge Mendes performed the statistical analysis, checked the analysis, and revised and co-wrote the article. Andreia Fonseca, Joana Barros, Sara Vargas, Diana Martins, Catarina Carvalho, Margarida Cal, and Inês Martins performed the ultra- sounds, recruited patients, checked the analysis,

and revised and co-wrote the article. Catarina Carvalho performed the ultrasounds, recruited patients, checked the analysis, and revised and co-wrote the article.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants but are available from the corresponding author.

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