SONOGRAPHIC EVALUATION OF FETAL GROWTH IN THE THIRD TRIMESTER OF LOW RISK PREGNANCY: A RANDOMIZED TRIAL

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Abstract

Objective

To evaluate the accuracy of 35-37 weeks` ultrasound for fetal growth restriction (FGR) detection and the impact of 30th-33rd weeks *vs* 35th-37th weeks ultrasound on perinatal outcomes.

Design

A prospective randomized trial

Setting

Tertiary referral hospital in Portugal.

Population

Low risk pregnant women

Methods

We enrolled 1061 women: 513 in the control group (ultrasound at 30th-33rd weeks) and 548 in the study group (with an additional ultrasound at 35th-37th weeks). FGR was defined as an estimated fetal weight (EFW) below 10th percentile. We calculated the overall accuracy of the 35-37 weeks' ultrasound and compared perinatal outcomes between both groups.

Main outcome measure

Detection of late FGR

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 cesarean deliveries for nonreassuring fetal status (16.8% *vs*

3

38.8%, $p < 0.001$). For FGR prediction, the area under the receiver-operating characteristics curve of EFW centile at 35-37 weeks' ultrasound was 0.90 (95% CI, 0.86-0.95).

Conclusions

A later ultrasound (35-37 weeks) had a higher correlation between EFW and birthweight centiles and was associated with a lower rate of cesarean and operative deliveries for nonreassuring fetal status compared to an earlier ultrasound, which reinforces that antenatal identification of FGR allows close monitoring and appropriate management.

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Keywords: Third-trimester screening, low risk pregnancy, fetal growth restriction, ultrasonography, estimated fetal weight, adverse perinatal outcome, cesarean deliveries, nonreassuring fetal status

Tweetable abstract

35-37 weeks scan was associated with less cesarean deliveries for nonreassuring fetal status than 30-33 weeks ultrasound.

4

Introduction

Sonographic estimation of fetal weight (EFW) during 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 ultrasound and the best gestational age to perform it. Evidence has not yet provided advantages on perinatal outcomes.[2] The main argument against a routine third trimester ultrasound 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 International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), screening for FGR is an essential component 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 30^{th}-33^{rd} weeks.[9] Nonetheless, data from ROUTE study, that was a randomized trial, showed that FGR detection rate was superior at 36 *vs* 32 weeks' gestation.[10]

The aim of this study was to evaluate the accuracy of 35^{th}-37^{th} weeks´ ultrasound for FGR detection and the impact on perinatal outcomes.

5

Methods

Patient recruitment and outcomes

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 nor in the writing of this report.

The population included in this study corresponded to low risk pregnant women referred by the Primary Care units to Hospital Universitário de Santa Maria, Centro Hospitalar Lisboa Norte, in accordance with local guidelines.

According to national guidelines, 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.

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; 4) absence of medical history of diabetes, autoimmune or renal diseases, 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

6

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 was collected at time of enrolment such as: maternal age, ethnicity, parity, height, weight, 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.

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 birthweight centile. Secondary outcomes were to compare perinatal data between study and control groups.

Ultrasound measurements

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

7

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 pellucidi. BPD was measured by outer-to-inner calliper 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. FL 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 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 (MCA) and uterine artery (UtA). The respective pulsatility index (PI) and cerebroplacental ratio (CPR) were registered.

Definition of FGR and monitoring

FGR was defined according to the American College of Obstetricians and Gynecologists (ACOG) as a fetus with an EFW below the 10th percentile and SGA as a newborn with a birthweight below the 10th percentile.[16]

8

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 < 10^{th} centile and normal Doppler - Doppler re-evaluation after one week of diagnosis and EFW + Doppler after two weeks. If Doppler is normal and the fetus remains on the same growth curve, ultrasound controls are performed every two weeks and delivery is scheduled at 39 weeks.
- FGR with EFW or AC < 3^{rd} centile or EFW < 10^{th} centile + UA IP > 95^{th} centile: weekly Doppler and CTG. EFW every two weeks. If normal Doppler in all evaluations, delivery is scheduled at 37 weeks.
- FGR with CPR < 5^{th} centile or MCA PI < 5^{th} centile; Doppler evaluation three times per week; CTG every eight hours; EFW every two weeks. If no additional Doppler anomalies in all evaluations, delivery is scheduled at 37 weeks.
- FGR with absent or reversed end diastolic flow in UA are indications for delivery at the gestational age of the ultrasound evaluation in the study group.

For all groups, in case of Doppler anomalies, they were confirmed within 6-12 hours. 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 centiles.

9

Nonreassuring fetal status was defined by the interpretation of continuous CTG, using the ACOG classification.[17]

Statistical analysis

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

Chi-square tests or Fisher's exact test and Students 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 35^{th}-37^{th} weeks (study group), the investigators would require a total sample of 1200 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

10

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 1093 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 1061 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 (birthweight < 10^{th} centile). Within the 52 cases of SGA in the study group, the ultrasound at 35-37 weeks` gestation detected 26 (50%). Although the rates of operative vaginal and cesarean deliveries were similar for the two groups, the study group had a lower rate of operative vaginal deliveries for nonreassuring fetal status (24.4% *vs* 39.3%, p = 0.005) and also 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.

Per protocol, 501 and 510 participants underwent an additional scan at 35 to 37 weeks´ gestation and were included in control group (followed the national recommendation of third trimester ultrasound at 30-33 weeks), respectively. Forty-seven (8.6%) participants did not attend the ultrasound that was scheduled for the study group. We tried to contact these patients by phone to reschedule the scan, but in 30 patients there was no date available to perform 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. Baseline characteristics were comparable between groups (Table S1). The rate of SGA was similar between

11

study and control groups [50/501 (10%) *vs* 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%) *vs* 52/134 (38.8%), $p = 0.003$] and also a lower rate of cesarean deliveries for nonreassuring fetal status [16/101 (15.8%) *vs* 40/103 (38.8%), $p < 0.001$), compared to control group (Table S1). 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 ≥ 10^{th} centile, the median gestational age at delivery was lower for the FGR group [39 (38-39.6) *vs* 40.1 (39.1-40.6), p <0.001].

Considering only the pregnant women that performed ultrasound at 35-37 weeks' gestation in the study group (n = 501), this exam detected correctly 26 cases of FGR that had been missed by the standard 30-33 weeks' gestation ultrasound and also correctly considered appropriate weight for gestational age 446 cases (EFW 10^{th} centile) that corresponded to newborns with appropriate weight for gestational age at delivery (birthweight 10^{th} centile), 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 birthweight centile ($\rho = 0.75$) than the correlation coefficient between the EFW centile at 30-33 weeks' ultrasound and birthweight centile ($\rho = 0.44$).

For prediction of FGR, area under the receiver-operating characteristics (ROC) curve (AUC) of estimated fetal-weight centile at 35-37 weeks' ultrasound was 0.90 (95% CI, 0.86-0.95) (Figure S1). Table S2 demonstrates the performance of the ultrasound for FGR detection.

Discussion

12

Main findings

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 this 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%.

Strengths and limitations

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 < 10^{th} centile at 35-37 weeks' gestation compared with EFW ≥ 10^{th} centile may reflect the different surveillance and management provided for the first group. Since national guidelines recommend 30-33 weeks' screening ultrasound, 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 serial scanning in the study group may have contributed to improve detection of FGR and perinatal outcomes.

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 30-33 weeks' and 35-37 weeks' gestation ultrasounds and also important clinical and statistical differences in meaningful perinatal outcomes. Recruitment of patients in only one hospital has contributed to slow recruitment and may hamper

13

generalization of the results but has also allowed us to have a very low rate of loss to follow up (2.9%).

Interpretation

In our series, the AUC 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 *vs* 32 weeks' gestation,[10] but without better perinatal outcomes.[2,10] For one instance, metanalysis have 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 outcomes.[10]

The higher correlation coefficient between EFW centile 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.[19,20] Furthermore, a later scan during 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.[21]

Some authors,[22,23] but not all,[24,25] have reported that reduced third trimester growth velocity is associated with an increased incidence of certain adverse pregnancy

14

outcomes. According to ISUOG guidelines and Delphi consensus, fetal growth analysis may help in the management of pregnancy.[8,26] 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.

Conclusions

To conclude, in a country that recognizes the value of routine third trimester ultrasound screening of FGR for low risk pregnancies, our data is 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. Furthermore, 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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15

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Disclosure of interests

The authors report no conflict of interest

Author contributions

CP had the idea for the study. CP, NC and LMG designed the study. CP, AF, JB, SV, DM, CRC, MC, IM, performed the ultrasounds and recruited patients. CP and JM performed the statistical analysis. CP wrote the first draft of the article. AF, JB, SV, DM, MC, CRC, JM, IM, NC and LMC checked the analysis, revised and co-wrote the article.

Details of Ethics Approval

The study was approved by the Lisbon Academic Medical Center Ethics Committee in November 2013 (reference number 387/13).

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16

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17

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18

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19

Figure legends

Figure 1: Flowchart summarizing selection and grouping of study and control groups

Figure S1: Area under the receiver-operating characteristics curve for ultrasound performed at 35th-37th week`s gestation for prediction of fetal growth restriction