Longitudinal changes of cardiotocographic parameters throughout pregnancy: a prospective cohort study comparing small-for-gestational-age and normal fetuses from 25 to 40 weeks

ABSTRACT

Objective: To compare longitudinal trends of cardiotocographic (CTG) parameters between small-for-gestational-age (SGA) and normal fetuses, from 25 to 41 weeks of pregnancy.

Methods: A prospective cohort study was carried out in singleton pregnancies without fetal malformations. At least one CTG was performed in each of the following intervals: 24-26weeks^{+6d}, 27-29weeks^{+6d}, 30-32weeks^{+6d}, 33-35weeks^{+6d}, 36-38weeks^{+6d} and >39weeks. Tracings were analyzed using the Omniview-Sisporto® 3.6 system. Cases with a normal pregnancy outcome, including a birthweight $\geq$10th percentile for gestational age, were compared with two groups of SGA fetuses: with birthweight <10th percentile (SGA<p10) and <3rd percentile (SGA<p3; a subgroup of the latter). Generalized linear mixed-effects models were used for analysis.

Results: A total of 176 fetuses (29 SGA) and 1265 tracings (202 from SGA fetuses) were evaluated. All CTG parameters changed significantly throughout pregnancy in the three groups, with a decreasing baseline and probability of decelerations, and an increasing average long-term variability (LTV), average short-term variability (STV) and accelerations. Baseline showed a more pronounced decrease (steeper slope) in SGA fetuses, being higher in these cases at earlier gestational ages and lower later in pregnancy. Average LTV was lower in SGA<p3 fetuses, but a parallel increase occurred in all groups. There was a considerable inter-fetal variability within each group.

Conclusion: A unique characterization of CTG trends throughout gestation in SGA fetuses was provided. A steeper descent of the baseline was reported for the first time. The findings raise

the possibility of clinical application of computerized CTG analysis in screening and management of FGR cases.

Keywords: antepartum; cardiotocography; gestational age; growth restriction; heart rate, fetal; longitudinal; small-for-gestational-age

Introduction

Fetal growth restriction (FGR) has been associated to an increased risk of several adverse perinatal outcomes (1). Therefore, fetuses with this condition are among the most closely surveilled, namely with antepartum cardiotocography (CTG) which is, not rarely, started very early in pregnancy.

Many studies have reported significant changes in the different CTG parameters throughout gestation (2-5) that seem to occur as part of the normal fetal maturation. As such, it is important to take gestational age into account when interpreting CTGs in growth restricted fetuses, so that a normal variation associated to gestational age can be distinguished from an abnormality due to fetal compromise.

On the other hand, an integrated surveillance approach with longitudinal serial assessments with Doppler and biophysical profile scoring (BPS) has been recommended (1, 6). However, longitudinal CTG changes throughout pregnancy have never been thoroughly characterized in growth restricted fetuses.

Most studies on FGR presenting CTG findings do not discriminate them by gestational age, despite the great disparity of gestational ages among the studied individuals (7-19). Moreover, from these studies, only two were longitudinal, and were not conducted with the aim of characterizing the longitudinal evolution of CTG parameters throughout pregnancy.

The objective of the present study was to compare the longitudinal evolution of CTG parameters between normal and small-for-gestational-age (SGA) fetuses, from 24 to 41 weeks of gestation, in order to contribute to a more accurate interpretation of this exam and management of these cases.

Methods

A prospective cohort study was carried out in the antenatal clinic of a tertiary care university hospital. Women with singleton fetuses and no malformations detected on second trimester ultrasound, were recruited between 24 and 26 weeks and 6 days of gestation, calculated by first trimester ultrasound performed between 11 and 14 weeks. At least one CTG with minimum duration of 30 minutes was performed in each of the following pregnancy intervals, until delivery: 24-26weeks^{+6}, 27-29weeks^{+6d}, 30-32weeks^{+6d}, 33-35weeks^{+6d}, 36-38weeks^{+6d}, and >39weeks.

All tracings were recorded using Doppler probes with Hewlett-Packard M1350A or M1351 fetal monitors (Philips Medical, Boblingen, Germany) and analyzed with the Omniview-Sisporto® 3.6 system for computer analysis of CTGs (Speculum, Lisbon, Portugal) (20, 21). Several CTG parameters were calculated, and defined as follows: 1) signal loss: percentage of fetal heart rate (FHR) signals with values under 30 beats per minute (bpm); 2) signal quality: percentage of FHR signals transmitted by the fetal monitor as having high quality; 3) baseline: estimated using a complex algorithm (20) that takes into account the histogram analysis of FHR values in stable segments with low variability; 4) accelerations: increases in the FHR above the baseline, lasting 15 to 120 seconds and reaching a peak of at least 15 bpm; 5) decelerations: decreases in the FHR under the baseline lasting at least 15 seconds, and with a minimal amplitude of 15 bpm; 6) average long-term variability (LTV): the mean of the differences between maximum and minimum FHR values in a one-minute sliding window, in segments not considered to be accelerations or decelerations; 7) average short-term variability (STV): the mean difference between adjacent FHR signals. No averaging or reduction of FHR signals is performed by the system.

Tracings with signal loss above 33%, or signal quality below 80% were excluded from further analysis. As the number of accelerations, decelerations and uterine contractions in a tracing depends on its duration, these events were averaged for a 30-minute tracing.

Cases with a normal pregnancy outcome were compared with two groups of SGA fetuses: with birthweight <10^{th} percentile for gestational age (22) (SGA<p10); and with birthweight <3^{rd} percentile for gestational age (22) (SGA<p3; a subgroup of the latter). A normal pregnancy outcome was defined when delivery of a live newborn, with no malformations occurred at 37 weeks or beyond, with birthweight ≥ 10^{th} percentile for gestational age (22), Apgar score at 5 minutes ≥ 7, umbilical cord artery pH ≥ 7.05 (when available), and no admission to the Neonatal Intensive Care Unit (NICU).

The progression of each CTG parameter over time was evaluated by generalized linear mixed-effects (regression) models (23), in order to include both population effects (fixed effects) and individual effects (random-effects). Linear models were found to be suitable for evaluating FHR baseline, average LTV, average STV and accelerations over time. Time was centered (by subtraction with 24, the initial studied gestational age) in order to ease calculations and interpretation of effects. Absence of decelerations was observed in 63% of tracings, so this variable required dichotomization, and a logistic regression model was applied to evaluate the probability of decelerations being present. The observations were grouped at the individual level (all observations for each fetus). Several regression models with different random effects structures and correlations, residual correlation matrices and residual variances, and time structures for the mean predictor up to order two were considered. Random effects were not considered for each of the three groups, as the interest relied on comparisons of one group against another. The fitting process maximized the restricted maximum likelihood function.

Model comparisons were based on the likelihood ratio test for nested models and on the Akaike Information Criteria (AIC) otherwise. Evaluation of the model assumptions and

goodness-of-fit were investigated by graphical analysis. For the final model of each FHR variable, the observations with an absolute value of the standardized residual greater than 3 were removed from the model, as it greatly improved the residuals normality. These eliminations affected less than 1% of the total sample size. For each CTG variable, comparisons between normal and SGA<p10 fetuses and between normal and SGA<p3 fetuses were assessed by two independent models; both were found to have the same structural form in the linear predictor and residuals variance-covariance matrix. Random effects on the final models were identified at the intercept and linear time coefficient (with a diagonal correlation structure) for FHR baseline and average STV, only at the linear time coefficient for average LTV, and only at the intercept level for accelerations and decelerations. The variance structure of errors included different standard deviations per group in the FHR baseline model, and an exponential function of the fitted values in the models for average LTV, average STV and accelerations.

For characterizing the study population, continuous normally distributed variables were described using the mean and standard deviation, and compared with the t-test for two independent samples. Continuous non-normally distributed variables were described using the median, minimum and maximum, and compared with the Mann–Whitney U test. Frequencies of categorical variables were compared with the Chi-square test or the Fisher´s exact test, as appropriate. Statistical analysis was performed with the R language and software environment for statistical computation, version 2.15.3 (24). Statistical significance was set at $p<0.05$.

The study was approved by the local research ethics committee, and all the patients signed an informed consent form. The authors complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research.

Results

From the 250 women recruited, 51 were lost to follow-up and 23 were subsequently excluded because the fetuses were neither SGA, nor did they fill the criteria for normal

pregnancy outcome. A total of 176 fetuses and 1265 tracings were included in the study, distributed by the three groups as shown in Table 1, which also displays the general characteristics of the study population. One to three CTGs were performed in each of the intervals above mentioned throughout gestation. As there were only three CTGs at 41 weeks, analysis was not undertaken for this week.

All CTG parameters changed significantly throughout pregnancy in the three study groups (normal outcome, SGA<p10, SGA<p3), and longitudinal trends were similar in all groups: baseline and the probability of decelerations decreased throughout pregnancy, while average LTV, average STV and number of accelerations increased (Figure 1, Table 2).

The longitudinal evolution of the baseline was significantly different when comparing SGA<p10 or SGA<p3 with normal outcome cases. SGA fetuses showed steeper slopes of descent (particularly the SGA<p3 group): baseline was higher at earlier gestational ages, an overlap between SGA and normal outcome cases occurred at 28-29 weeks, and it became lower in the former thereafter (Figure 2, Table 2).

Regarding average LTV, the evolution over time showed parallel curves in the three groups (Figures 1 and 2), but values were lower in SGA fetuses, although the difference was only statistically significant for the comparison SGA<p3 vs. normal outcome (Table 2). For average STV, no significant differences between normal and SGA fetuses were identified (Table 2). The evolution curves were therefore similar (Figure 1). Likewise, there were no significant differences between the groups in the number of accelerations and in probability of occurrence of decelerations (Figure 1, Table 2).

There was a considerable inter-fetal variability for all CTG parameters in the three groups, although less evident for STV and accelerations (Figure 1).

Discussion

All CTG parameters changed significantly throughout pregnancy in SGA<p10, SGA<p3 and normal outcome cases, with a decreasing baseline and probability of decelerations, and an increasing average LTV, average STV and accelerations. Baseline showed a significantly steeper slope of decrease in SGA fetuses. Average LTV was lower in SGA<p3 fetuses, but a parallel increase throughout pregnancy was observed in all groups.

This is one of the largest and most complete studies to characterize the longitudinal behavior of CTG parameters in SGA fetuses throughout pregnancy. Even though, we recognize that the number of SGA fetuses is limited, and may have hampered further characterization of the groups and their differences.

The lack of information on Doppler indices and other biophysical parameters must be considered a limitation. There is not consensus on the terminology and diagnostic criteria for FGR, but the most widely used definition in the United States is an estimated fetal weight (EFW) <10^{th} percentile for gestational age (25). However, the Royal College of Obstetricians and Gynaecologists (RCOG) considers that fetuses with an EFW or abdominal circumference (AC) <10^{th} percentile, as well as infants with a birthweight <10^{th} percentile are SGA, which is different from of FGR (26). Growth restriction would involve a pathological restriction of the genetic growth potential, and possible manifestations of fetal compromise (as Doppler or BPS changes), being the likelihood of FGR higher in severe SGA cases, defined as an EFW, AC or birthweight <3^{rd} percentile (26). In the present study, the analysis of the SGA<p3 group greatly increased the likelihood of including FGR cases according to the RCOG concept. Differences in comparisons between normal and SGA<p10 were even more pronounced when the normal outcome group was compared to SGA<p3 fetuses, reinforcing the idea that they were associated with low fetal weight.

Nijhuis et al (27) evaluated longitudinally 27 FGR cases (135 CTGs), and although not clearly specified, appear to have also observed a decreasing trend in the baseline, as well as an increasing long and short term variation in FGR cases. Soncini et al. (28) studied 50 FGR cases (186 CTGs), and used correlation analysis to show that a decreasing trend in baseline occurred only in the less compromised fetuses, and was not seen when umbilical artery (UA) end-diastolic flow abnormalities were present; linear regression analysis showed a less pronounced descent (slope of the correlation line) in the latter set of fetuses. Likewise, the typical increase in FHR variability indices throughout gestation occurred in fetuses with no or mild Doppler velocimetry abnormalities, however in more compromised fetuses the correlation of STV and gestational age was mild, and not significant for other FHR variability indices; linear regression analysis showed a less pronounced slope for all FHR variability indices in fetuses with UA end-diastolic flow abnormalities (28). The correlation between increased total accelerations and gestational age was significant only in fetuses with increased/normal UA PI and preserved end-diastolic flow (28).

In the current study, all FHR variables in SGA fetuses presented the same increasing or decreasing trend as normal fetuses, and the only difference in time evolution was found in FHR baseline, with a more pronounced descent in SGA fetuses, particularly in the SGA <p3 group. As we did not have information on Doppler parameters, we could not go further in trends´ characterization as did Soncini et al. (28), however, the more evident differences in the SGA<p3 group pointed to a steeper slope with worsening fetal condition, which seems to be in opposition to what was reported in the latter work (28). In that study, despite the description of longitudinal trends, data was analyzed as if it was a cross-sectional study not taking into account the longitudinal evolution of each fetus, and the existence of at least two tracings per fetus was enough for inclusion. The two studies mentioned above used different systems for computer

analysis of tracings (Nijhuis et al (27), the Sonicaid System 8000® or 8002®; Soncini et al (28), the HP2CTG system) which may also have contributed to different results.

It is considered that there is a delay in maturation in biophysical milestones in FGR (29, 30), with higher baseline (27, 31), decreased variability (7, 11, 15, 27, 31, 32) and delayed development of reactivity (accelerations) and behavior patterns (8, 27, 32). This may be related to chronic hypoxemia and may possibly be explained by changes in myelination and central neurotransmiter availability (30). In the present study baseline was lower in SGA fetuses, particularly at latter gestational ages, contrary to what was previously reported, but the lower average LTV in SGA fetuses, was in agreement to what has been described. It has been suggested that the sympathetic nervous system is more affected than parasympathetic tone in FGR (8, 33), with a relative increase of parasympathetic influence (16). It has been pointed as a possible explanation for the delayed development of reactivity and the reduced FHR variability in FGR, and may also contribute to understand this FHR baseline behavior. Recently, Graatsma and co-workers used a technique to make a separate characterization of sympathetic and parasympathetic modulations of FHR in SGA fetuses suggesting that it may provide valuable information for recognition of compromised fetuses (33).

We did not try to identify rest and activity cycles on the basis of FHR pattern alone, because that is unreliable before 35 weeks (39). The median CTG duration in this study is around 30 minutes; the mean duration of quiet cycles is 20 minutes, although they may last up to 40 to 50 minutes (40, 41). Despite their limitations, the Sonicaid system´s episodes of low and high variation may be indicators of the fetal rest-activity cycles, and it is known that episodes of low FHR variation > 50 min are extremely unlikely for normal fetuses (10, 42, 43) (only 0.2% in one series (10)). Moreover, one of the system´s criteria for normality is the presence of at least one episode of high variation (43), and in one large study of healthy fetuses, the normality criteria were met in 97.7% of the tracings, despite their median duration of 12.0

min (10). Therefore, we believe that CTGs´ duration in our study was appropriate, and that most recordings were representative of both rest and activity cycles.

In conclusion, this study provides a unique approach to the characterization of the evolution trends of CTG parameters throughout gestation in SGA fetuses. It is the first one to report a steeper slope of baseline descent in SGA fetuses, and together with the finding of a lower average LTV, supports the hypothesis of a more severe compromise of the sympathetic nervous system in this population. These findings open the opportunity for a more accurate characterization of the CTG with techniques that allow a separate analysis of both components of the autonomic nervous system. The divergent baseline behavior of SGA fetuses may be revealed by sequential evaluation of CTG tracings, and could prove to be useful for screening of this condition. Studies with a larger number of SGA fetuses and with information on Doppler variables and long-term outcome are required to determine whether longitudinal evaluation of CTG parameters may be of help in the decision to deliver these cases.

Acknowledgments

The authors would like to thank all prenatal outpatient clinic staff, in particular the nurses, for their assistance in data collection. The authors would also like to thank Cristina Costa Santos, MSc, PhD for her contribution to data analysis.

Funding

A. Rita Gaio was partially supported by CMUP (UID/MAT/00144/2013), which is funded by FCT (Portugal) with national (MEC) and European structural funds through the programs FEDER, under the partnership agreement PT2020.

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Tables and figures – legends

Figure 1. Predicted time evolution of each cardiotocographic parameter throughout pregnancy, in cases with a normal pregnancy outcome (N outcome), small-for-gestational-age fetuses with birthweight <10th percentile (SGA<p10) and <3rd percentile for gestational age (SGA<p3; a subgroup of the latter). Black lines correspond to the fitted individual curves; the red lines represent the mean predicted time evolution of the whole group. For decelerations, the predicted probability of having decelerations is represented.

Footnote: Different models were used for comparisons N outcome vs SGA<p10 and N outcome vs SGA<p3. As no evident differences between the plots obtained with different models were identified for N outcome cases, only the curves derived from the models used for N outcome vs SGA<p10 comparisons are presented.

Figure 2. Comparison of the mean predicted time evolution of baseline and average long-term variability between cases with normal pregnancy outcome (N outcome, solid lines) and small-for-gestational-age fetuses (SGA, dotted lines), with birthweight <10th percentile (SGA<p10) and <3rd percentile for gestational age (SGA<p3; a subgroup of the latter).

Table 1. General characterization of the analysed groups: normal outcome cases (N outcome), and small-for-gestational-age fetuses, with birthweight <10th (SGA<p10) and <3rd percentile for gestational age (SGA<p3, a subgroup of the latter). Comparisons were N outcome vs SGA<p10 and N outcome vs SGA <p3.

Table 2. Estimates from the obtained models comparing normal outcome cases (N) with small-for-gestational-age fetuses with birthweight <10th (SGA<p10) and <3rd percentile for

gestational age (SGA<p3; a subgroup of SGA<p10). Comparisons were N vs SGA<p10 and N vs SGA <p3.