Fetal heart rate and nuchal translucency as first trimester markers of preterm birth.

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ABSTRACT

Objective

To evaluate whether first trimester fetal heart rate (FHR) and nuchal translucency (NT) associate with preterm birth (PTB).

Methods

This was a comparative case-control study of 518 normal pregnancies with no history of PTB of which 272 delivered at term (TB) and 246 progressed to spontaneous PTB prior to 37, 34, 32 and 28 weeks. Fetal heart rate (FHR) and nuchal translucency (NT) values at the first trimester scan were compared by means of univariable (Mann-Whitney) and multivariable logistic regression analysis considering hourglass membranes (HM) as the most severe PTB subgroup. Finally severity trends for both parameters were investigated using correlations with gestational age (GA) at delivery and Kruskal-Walls tests.

Results

Regardless of GA at delivery, pregnancies affected with PTB showed higher FHR and thicker NT at the first trimester scan. The association was confirmed by the multivariable analysis and the severity trends, which paired the highest FHR and NT values with the most severe cases of PTB ($p<0.001$) ($p<0.0001$).

Conclusion

Fetuses with subsequent late, early and very early PTB show higher values of NT and FHR at the first trimester scan.

KEY WORDS

Preterm birth, fetal heart rate, first trimester screening, nuchal translucency.

INTRODUCTION

Preterm birth (PTB) occurs in 10% of the world pregnancies [1,2]. However its incidence varies according to the wealth and socioeconomic situation of the different countries: in the underdeveloped world, including India and most African countries, it approaches 20%, while in Europe and North America its incidence is closer to 5 % [1,2], a figure that has been increased after the advent of assisted reproduction and its repercussion on the number of multiple pregnancies [3,4]. Unfortunately, although management of PTB has notably improved with the use of lung maturation and utero-inhibitory drugs, it still present dreadful lifelong consequences derived from neurological complications of prematurity [5].

Most of PTB is of unknown origin. However, the hypothesis of inflammation [6-8] as a key mechanism triggering contractions and cervix effacement, which also occurs in term labor [9,10] has gained increasing importance. Moreover, treatment with antibiotics has proven to be useful at early stages, eradicating a proportion of cases with PTB, intact membranes, and intra-amniotic inflammation [11].

Interestingly, diabetes [12-14] and dental infections [15-17] may also lead to PTB, probably through a similar activation of the inflammatory cascade that could theoretically modify diverse biological parameters such as fetal heart rate (FHR) and heart performance [18-23]. In fact, higher FHR values in the first trimester were observed in association with type I diabetes [24]. In his regard, we hypothesized whether the FHR increase could be caused by maternal inflammation due to chronic diabetes and whether the scenario leading to the FHR increase could be resembled in case of inflammation causing preterm birth. In this work we aimed to evaluate first trimester FHR as a possible marker for PTB along with nuchal translucency, a well-known first trimester marker of adverse pregnancy outcome, also related with PTB [25].

MATERIAL AND METHODS

This was a comparison study of two groups of normal pregnancies (N=518) with no history of PTB of which, 272 were delivered at term, 37 weeks or more, (TB) and 246 progressed to spontaneous PTB. In both groups, data from the first trimester scan were collected, including FHR, nuchal translucency (NT), gestational age (GA) at examination, maternal age, weight and height, parity, number of gestations, smoking and type of conception (spontaneous or assisted reproduction). Finally, data related with birth were also documented, including the type of event leading to labor onset (term contractions, preterm contractions, preterm PRM followed by contractions and hourglass membranes (HM)) and the GA at which this event started, the via of delivery (vaginal, assisted vaginal, cesarean due to dystocia and cesarean due to abnormal CTG), birth weight (BW), birth weight centile, fetal sex, Apgar score at 5 minutes, arterial pH, and baby destiny (maternal ward, neonates ward and intensive care pediatric unit).

PTB was defined as any spontaneous onset of labor prior to 37 weeks [26]. In some cases, patients debuted initially with uterine contractions and subsequent cervical shortening. In others, they debuted with preterm rupture of membranes (PRM) and subsequent contractions. Finally, a few cases started as hourglass membranes (HM) delivering at very early GA representing the PTB subgroup with the highest severity. PRM was defined as the rupture of amniotic membranes prior to 37 weeks, while HM was defined by the presence of bulging membranes through the cervical external os at the speculum examination, usually with slight spotting and absent or minor uterine contractions. In all cases and to ascertain the diagnosis, HM were also visualized with transvaginal ultrasound. All HM cases either delivered spontaneously without obstetrical intervention or finished in late-term miscarriage (<24 weeks).

As per local protocol, and in line with international guidelines, prior to 34+6 weeks, cases of PTB starting with uterine contractions were treated with intravenous atosiban (Tractocile®) plus betamethasone (Celestone®) to achieve lung maturation [26,27]. In addition, cases with PRM were treated with triple antibiotic therapy (ampicillin 1g/6 hours, gentamicin 80 mg/8 hours and azitromicin 1g single dose), lung maturation and induction over 34 weeks.

Finally, prior to 32 weeks intravenous magnesium sulphate was also administered as neuroprotectant in order to diminish the possibility of brain damage and neurological sequelae.

In order to study the possible relationships with PTB, all pregnancy characteristics were analyzed, describing their means, standard deviations (SD), medians and interquartile ranges (IQR) (25%-75%). Subsequently, the existence of differences between TB and PTB groups was assessed by mean of univariable analysis. In addition, correlations of FHR and NT with GA at birth were performed and severity trends were investigated. Finally, multivariable logistic regression analysis were calculated to confirm the associations between these parameters and PTB prior to 37, 34, 32 and 28 weeks and HM, describing the Odds ratios (OR), OR 95% confidence intervals (OR 95% CI) and P-values.

Comparisons were made with Mann-Whitney U tests for continuous data and Fisher´s exact tests for frequency data. Severity trends for NT and FHR were evaluated by mean of Kruskal-Wallis tests and correlation was done using Pearson Coefficient R^2. Statistical analysis and graphs were done with StatPlus® for Mac, version 7 and GraphPad Prism® for Mac, version 5. Significance was established at a P-value below 0.05.

RESULTS

The characteristics of the study population are shown in table 1. In summary, it included 518 fetuses, of which most (51.1%) were of male sex and delivered at term (52.5%). The mean maternal age, gravidity, parity and BMI were 32.3, 2.1, 0.6 and 24.1, and the mean GA at examination, labor onset and delivery 12.4, 36.9 and 37.1 weeks. All pregnancies initiated labor spontaneously, delivering mostly vaginally (73.5%). In most cases, neonates were born uneventfully and accompanied the mother to the maternity ward (79.5%). Moreover, only 1.3 % had an Apgar score below 7 at 5 minutes, while 3.9% had neonatal cord pHs below 7.10. Although 55.8% needed admission to postnatal pediatric care, the proportion of fetuses below the 10th centile was close to the general population (14.1%).

Table 2 compares PTB and TB characteristics. In summary, PTB fetuses (N=246) presented higher NT ($p<0.0001$) and FHR ($p=0.0017$) values and a higher frequency of smoking ($p=0.0256$) Apgar score below 7 at 5 minutes ($p<0.0001$), scheduled cesarean section ($p=0.0111$), smallness for gestational age ($p=0.0225$), pediatric admission ($p<0.0001$) and male sex ($p<0.0001$).

Figure 1 compares FHR and NT values between TB and PTB fetuses delivering at different GA (<37, <34, <32, <28 and HM). FHR and NT differences were significant at all GA ($P<0.05$ to $P<0.0001$). In addition a severity trend was observed for both parameters ($P<0.001$, $P<0.0001$), with higher FHR and NT values in the most severe cases of PTB (HM). Moreover, both, FHR and NT, correlated with GA at PTB ($R^2=0.016$, $P<0.05$ and $R^2=0.042$, $P<0.0001$).

Finally, table 3 describes the multivariable logistic regression analysis studying the associations of several parameters, with PTB at different GA. Both parameters, NT and FHR, were selected as independent determinants of PTB ($P<0.0001$ to $P<0.05$ and $P<0.01$ to $P<0.05$ depending on GA) and maintained this condition at all degrees of PTB severity.

DISCUSSION

Summary of findings

This study shows that first trimester NT and FHR associate with late, early and very early PTB, and that this association shows for both parameters a severity trend.

Comparison with existing literature

This is the first study to describe the association of FHR and NT with PTB.

Our data agree with previous reports suggesting that high NT values associate with different adverse outcomes, including PTB [25, 28]. However in these works information provided by FHR was not included. They are also in line with previous reports showing the association of PTB with several maternal and fetal characteristics, like body mass index [29], smoking [30], male sex [31] and assisted reproduction [32].

We did not found a clear physiopathological explanation for the association of TN and FHR with PTB, apart from the general association of NT with adverse outcome [25]. However, as PTB has been frequently related with inflammation [6-8], we hypothesized the possibility to link this condition with those changes observed in FHR, in analogy to those seen in type I diabetes, a chronic process, which interestingly has also been related with both PTB and fetal and mother FHR variations [12,13,23,33-38].

Several relationships support a plausible role of inflammation on FHR: First, chronic diseases and maternal poor health cause inflammation, increasing the incidence PTB [39,40]. Second, preterm and term labor have been related with an increase of pro-inflammatory cytokines in the fetal [41,42] and maternal [43] compartments. And third, cytokines produced during inflammation have been associated with heart rate changes, including tachycardia and changes of variability [18-22]. Consequently, it would be possible to expect relationships between FHR, cytokines and PTB. In addition, we have suggested a correlation between ultrasound changes, and severity of PTB, which might suggest a role for the intensity of inflammation in the promptness of PTB.

Clinical implications

Prediction of PTB is currently based on cervical length measurement at 20 weeks [44]. However, cost-effectiveness studies are still controversial and the

efficacy and implementation protocol is under debate [45,46]. This work suggests the theoretical possibility to screen for PTB earlier in pregnancy, using data collected in the entire fetal population during the 12 weeks scan. The information obtained might be used to stratify risks and define the access to PTB prediction at 20 weeks using cervical length.

Strengths and weaknesses

The strengths are the accurate statistical methodology, and especially its novelty, as there are no previous studies evaluating the association of PTB in the first trimester with simple data available at the 12 weeks ultrasound. Of note, NT and FHR kept their importance throughout all GA proving that whatever might be the mechanism triggering PTB, both cardiovascular parameters are called to play a role as PTB markers. Shortcomings include the retrospective nature of the study and the different importance of the different maternal parameters, which might be due to the moderate number of cases included.

Conclusion

Fetuses developing PTB show higher values of NT and FHR at the first trimester scan. Future studies are needed to validate these results and evaluate these parameters as possible markers of PTB.

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Statement of ethics

Being a retrospective study in which all data were collected during the routine clinical management there was not a need to obtain informed consents. However an IRB authorization was obtained for the study (Reference 2014/0063).

Conflict of interest statement:

The authors report no conflict of interests.

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Author Contributions:

José Morales-Roselló did the study design, collected cases, performed the statistical analysis and wrote the manuscript.

Gabriela Loscalzo, Gemma Perez, Alicia Soriano and Vaidilė Jakaitė collected cases and participated actively in the review of the manuscript.

Alfredo Perales Marín

Contributed to the study design and participated actively in the review of the manuscript.

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FIGURES

Figure 1. (Upper left) First trimester FHR values in TB and PTB fetuses delivering prior to 37, 34, 32, 28 weeks. **(**Upper right) First trimester NT values obtained in TB and PTB fetuses delivering prior to 37, 34, 32, 28 weeks. In both cases HM was added as the group with highest severity and earliest PTB. (Lower left) Correlation between FHR and GA at birth. **(**Lower right) Correlation between NT and GA at birth.