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ORIGINAL ARTICLE

Changes in short-term variation of antenatal cardiotocography to identify intraamniotic infection: a historical cohort study

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ABSTRACT

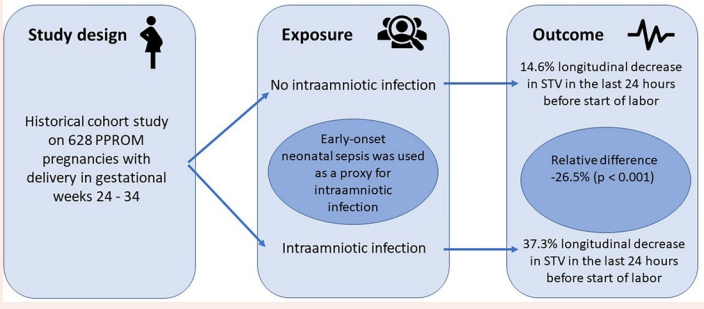
Introduction: Intraamniotic infection (IAI) is one of the main possible complications of preterm prelabor rupture of membranes (PPROM) and can lead to severe consequences for the neonate, such as early onset neonatal sepsis (EONS). Available diagnostic tools for IAI have poor diagnostic performance, which may result in both over- and underdiagnoses of IAI. In a search for better diagnostic tools, we have examined short-term variation (STV) in fetal heart rate. We have previously shown that in IAI exposed pregnancies, the STV was more than 20% lower in the last cardiotocography trace before the start of labor, as compared to those not exposed to IAI. The association between IAI and STV needs further evaluation and we therefore continued by examining the longitudinal change in STV in association with IAI.

Material and methods: We performed a historical cohort study on 628 singleton pregnancies with PPROM, delivering between 24+0 to 33+6 gestational weeks. The main exposure of the study was IAI, using EONS as a proxy as no easily available method exists for confirming IAI antepartum, and IAI and EONS are strongly associated. The main outcome was STV in fetal heart rate. At least two available cardiotocography traces per fetus were required as a minimum, from PPROM or from seven days before birth, whichever came later, until the start of labor or planned cesarean birth. A total of 9 690 cardiotocography traces were analyzed.

Results: Fetuses exposed to IAI had a 26.5% steeper decline in their STV during the last 24 h before the start of labor when compared to fetuses not exposed (95% CI −32.9% to −19.4%; $p < 0.001$). After adjustment for antenatal corticosteroids, the decline remained significant. The decline became less prominent but the significance remained when also adjusting for the baseline frequency (−12.7% [95% CI −19.3% to −5.5%], $p < 0.001$). In the IAI-exposed group, the baseline frequency increased by 11.1 bpm during the last 12 h before the start of labor, beyond those who were not exposed (95% CI 8.3 bpm to 13.8 bpm; $p < 0.001$).

Conclusions: In pregnancies affected by IAI the STV declines steeper in the last 24 h before the start of labor as compared to pregnancies not affected by IAI, even after adjustment for increasing baseline frequency. The association of STV in relation to IAI needs to be further studied in order to evaluate and establish STVs usefulness in monitoring patients for IAI.

GRAPHICAL ABSTRACT



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KEY MESSAGE
In pregnancies with preterm premature rupture of membranes, short-term variation decreases significantly steeper during the last 24 h before the start of labor in pregnancies complicated by intraamniotic infection when compared to pregnancies not affected.

Introduction

Intraamniotic infection (IAI) is a microbial infection of the amniotic fluid, fetus, placenta, fetal membranes and/or the decidua [1,2]. Preterm prelabor rupture of membranes (PPROM) increases the risk of IAI, with up to 50% of patients having either positive culture or polymerase chain reaction analysis in their amniotic fluid [3,4]. With IAI, bacteria can enter the fetus by the lungs, gastrointestinal tract, skin, eyes and ears. IAI increases the risk of severe complications for neonates, including early onset neonatal sepsis (EONS), bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy and intraventricular hemorrhage [5–9].

In the absence of contraindications to continuing pregnancy after PPROM, expectant management leads to better maternal and neonatal outcomes when compared to planned early birth [10]. An important contraindication for expectant management is IAI, and therefore women have to be closely monitored for signs of IAI. This monitoring is performed through clinical assessment of maternal symptoms and vital parameters, blood tests (C-reactive protein and the white blood cell count) and fetal surveillance. Unfortunately, these diagnostic tools have poor diagnostic performance for IAI [11–14], making it difficult for the clinician to assess the development of IAI and to induce delivery in a timely manner.

Further research on and use of antenatal cardiotocography (CTG) has been suggested for the purpose of IAI monitoring and diagnosis. Our research group recently published a cohort study showing an association between IAI and short-term variation (STV) in fetal heart rate, with fetuses affected by IAI having a 20.5% lower STV in the last CTG trace before the start of labor compared to those not affected by IAI [15]. Previously, the relationship between STV and IAI has only been scarcely studied and knowledge regarding how and when IAI affects STV is lacking. We therefore wanted to explore this association further to gain better insight into the possible use of CTG as an aid in the diagnosis of IAI. The aim of the current study was to analyze the longitudinal change in STV during the latency period from PPROM to delivery and compare those affected by IAI to those not affected.

Methods

In this historical cohort study, we included all singleton pregnancies with PPROM, resulting in a live-born offspring delivered from 24 + 0 to 33 + 6 gestational weeks in Stockholm County, Sweden, between 2012 and 2019. Exclusion criteria were insufficient data, intrauterine fetal death and fetuses/neonates with any kind of cerebral malformation, as STV is mainly controlled by the autonomic nervous system. Pregnancies with less than 12 h between PPROM and birth were also excluded in order to omit cases where the rupture of the membranes was part of impending labor.

The main exposure of the study was IAI. When studying IAI, especially in the retrospective study setting, a proxy is often used since no easily available method exists for confirming IAI antenatally. Histological chorioamnionitis has often been used as a proxy. Although correlated with IAI, histological chorioamnionitis is not necessarily caused by intraamniotic infection as it can be observed in the absence of both positive microbiology and biochemical markers for inflammation, even in preterm pregnancies [16–19]. Also, the prevalence of histological chorioamnionitis at the time of delivery is more than 50% in women with PPROM [20,21] and its association with neonatal outcome is unclear [22,23]. Histological chorioamnionitis may therefore not be an ideal proxy for the exposure IAI. We consider the development of EONS, defined as occurring within 72 h after birth, to be a better proxy. EONS is considered to be caused by vertically transmitted pathogens from the mother to the infant, and IAI and EONS are strongly associated with most preterm infants with EONS being born to mothers with IAI [9,24,25]. We therefore found EONS to be an attractive proxy for IAI when studying the association between IAI and STV. The diagnostic criteria used for EONS were the presence of three or more clinical symptoms (respiratory, circulatory, neurological, gastrointestinal or hematological), at least one laboratory test indicating infection (white blood cell count $< 5\times10^9$/L, neutrophil count $< 1.5\times10^9$/L, platelet count $< 100\times10^9$/L or C-reactive protein concentrations > 20 mg/L) and treatment with antibiotics for at least five consecutive days [26].

The main outcome of the study was the longitudinal change in STV. The fetal heart rate was recorded

with one of the following monitors: Sonicaid™ (Huntleigh, United Kingdom), Avalon™ (Philips, Netherlands) or EDAN™ (EDAN Instruments, China). Our research group has previously developed an algorithm implemented in MATLAB 2022a (MathWorks Inc., Natick, MA, USA), enabling extraction of mean STV and mean baseline frequency from existing CTG traces. The algorithm, described in detail in previous publications [27,28], calculates the STV according to the Dawes/Redman algorithm, dividing each minute of a CTG trace into 16 segments of 3.75 s [29]. For each segment, the average pulse interval is calculated in milliseconds. The STV is the average difference in pulse intervals between consecutive segments within each minute. For the STV calculations, decelerations in fetal heart rate were excluded according to the Dawes/Redman algorithm, as were segments with more than 10-min continuous signal loss. As a secondary outcome, we analyzed the longitudinal change in baseline frequency.

All available CTG traces from PPROM or from seven days before birth, whichever came later, until start of labor or cesarean delivery, were analyzed. If labor was induced, CTG traces were included until the labor started. A minimum of two CTG traces for each fetus was required. CTG traces exceeding 30 min were divided into 30-min segments. We excluded CTG traces with a mean baseline frequency below 110 beats per minute (bpm) to exclude traces likely affected by other mechanisms such as hypoxia or arrythmia. After scrutinizing a scatter plot, STV values >30 ms were also excluded due to likely errors in the calculation [28,30–33].

To compare the groups with and without IAI, we collected data from electronic medical records, registered prospectively during antenatal and peripartum care. Background data of interest were maternal age, body mass index, smoking status, parity, diabetes, hypertension and preeclampsia. Timepoints of PPROM, administration of antenatal corticosteroids, start of labor and time of birth were documented. The birthweight of the neonate was recorded as well as its sex, Apgar scores, umbilical artery cord blood gas analysis and whether the neonate was small for gestational age (defined as weight below two standard deviations from the mean birth weight of the current gestational age) [34].

PPROM was diagnosed by clinical presentation and a sterile vaginal speculum examination searching for leakage of amniotic fluid. Some of the delivery units used a test for placental alpha microglobulin-1 protein (Amnisure®; AGHealth Ltd., London, England) to confirm the diagnosis. Women with confirmed PPROM were admitted to inpatient antenatal unit. Initially they were treated with antibiotics (oral erythromycin or clarithromycin for 10 days) and corticosteroids (12 mg betamethasone, two doses 24 h apart). Thereafter they were managed expectantly until 34–37 gestational weeks in the absence of spontaneous labor or indications for planned early birth, such as suspected intraamniotic infection, placental abruption or signs of fetal distress. At the time of PPROM, urinary culture was recommended as well as a chlamydia test, CTG, blood test (white blood cell count and C-reactive protein) and fetal ultrasound. During the expectant management, the women were monitored for signs of IAI with clinical assessment of maternal symptoms and vital parameters, blood tests, ultrasound and CTG. The frequency of these controls was dependent upon maternal and fetal factors such as gestational week and results of initial tests. In this study, only women who delivered before 34 gestational weeks were included since timing of planned delivery after PPROM varies after this time in different obstetrical units. During preterm labor, the women received intravenous penicillin as a prophylaxis against Group B *Streptococcus*.

Statistical analyses

The baseline characteristics were estimated and compared for the exposed IAI group and the non-exposed group. Continuous data were summarized as the median and interquartile range and tested using the Mann–Whitney U test. Categorical data were summarized as percentages and tested using Pearson's chi-square test.

The longitudinal development of mean STV and baseline frequency was visualized using locally estimated scatterplot smoothing curves, weighted against the inverse of the total number of measurement points for each fetus. Crude and adjusted linear mixed models with random intercepts were applied to estimate changes in mean STV and baseline frequency over time. An unstructured covariance structure was used, and observations were weighed against the inverse of the total number of measurement points for each fetus. Due to the residuals in the model not being normally distributed for the STV values, analysis of STV was performed using log-transformed values, resulting in estimates of relative change. For baseline frequency, results are displayed as the absolute values. Time to start of labor was modeled in segments with segment breaks placed based on visual impression of the initial analysis of the locally estimated scatterplot smoothing curves. None of the variables used for statistical analyses had missing values.

In the adjusted linear mixed models for change in STV we have adjusted for baseline frequency and antenatal corticosteroids, which we consider as potential confounders in our longitudinal STV analysis. Baseline frequency can increase with the exposure IAI, and the outcome STV and baseline frequency are negatively correlated [35–37]. Baseline frequency therefore lies in the causal pathway between IAI and the longitudinal change in STV. Antenatal corticosteroids are known to affect the outcome STV for 24–72 h after administration [38–40]. Antenatal corticosteroids have not been shown to increase the risk for the exposure IAI [41], but they can possibly increase the risk for the neonate developing infection [42,43]. This includes EONS which is our proxy for IAI. Therefore, antenatal corticosteroids could be considered a confounder. Adjustment was made for those if given 24 to 72 h before the start of the current CTG trace. We did not adjust for covariates that are constant within each individual, such as smoking, diabetes and fetal sex, as we are exploring the longitudinal development of STV within the individual and covariates constant within the individual are caught within the random intercept of the linear mixed model. Gestational age is nearly constant during the seven-day period we are examining the longitudinal STV change, but in order to examine whether the longitudinal change is the same across different gestational ages, we stratified the cohort into two groups with gestational ages above or below 30 gestational weeks.

In the analysis of the secondary outcome of baseline frequency, we adjusted for antenatal corticosteroids, considering those as a possible confounder in light of the above-mentioned possibility that they

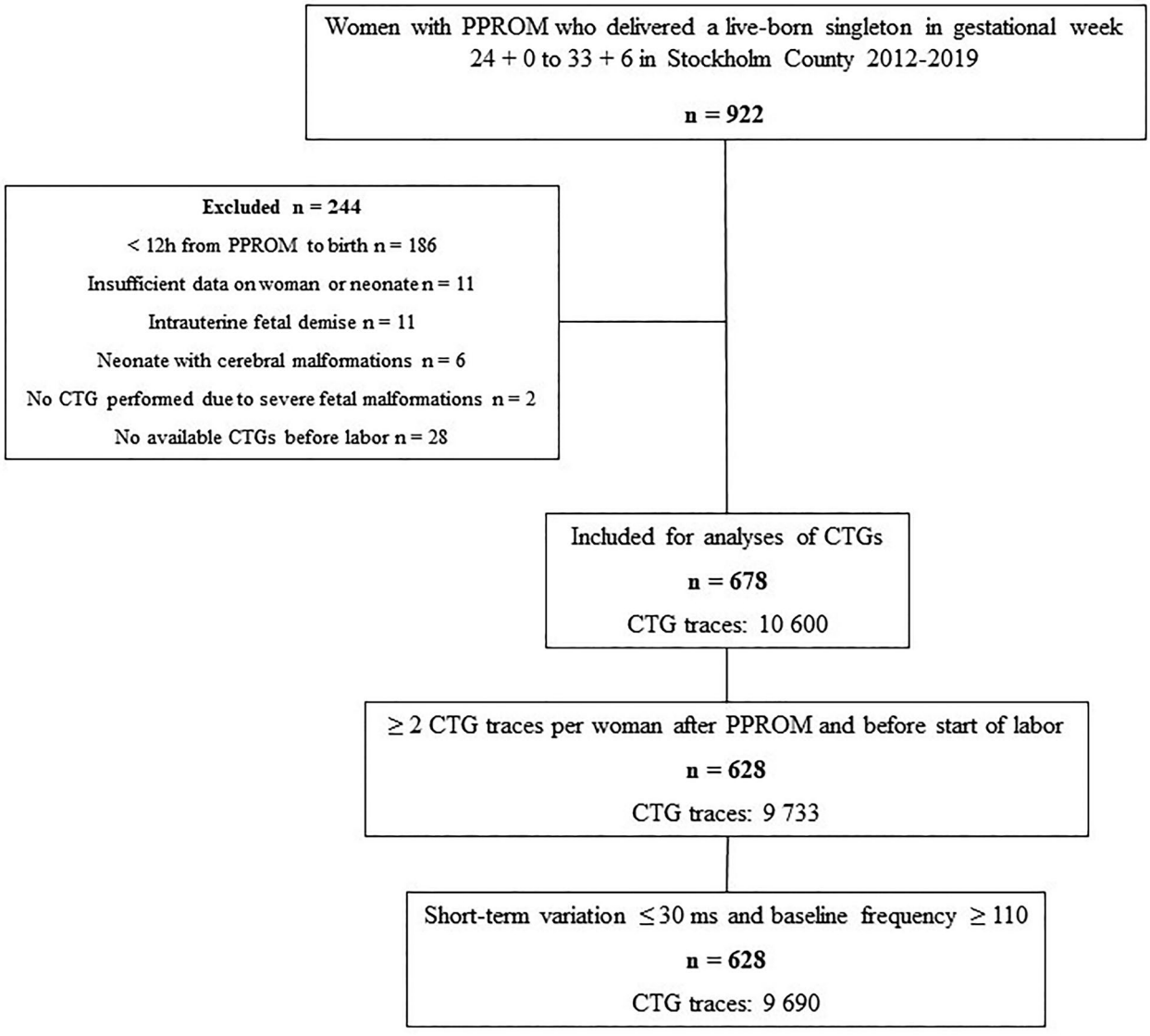

Figure 1. Flow chart showing study population selection.
Abbreviations. PPROM, preterm prelabor rupture of membranes; CTG, cardiotocography

Table 1. Maternal and neonatal characteristics, comparing groups exposed and non-exposed to intraamniotic infection, using early-onset neonatal sepsis as a proxy for intraamniotic infection. Data are presented as medians with interquartile ranges, or as percentages.

	No intraamniotic infection ($n=605$)	Missing (n)	Intraamniotic infection ($n=23$)	Missing (n)	p value[a]
Maternal characteristics					
Age (years)	33 (29–36)	0	32 (28–35)	0	0.645
Body mass index (kg/m^2)[b]	23.2 (21.1–26.8)	58	25.2 (21.8–28.2)	3	0.147
Smoking[b]	5.5%	44	14.3%	2	0.093
Parity: 0, 1, 2+	30.4%, 43.6%, 26.0%	0	39.1%, 30.4%, 30.4%	0	0.446
Gestational age at PPROM (weeks)	30.6 (27.7–32.6)	0	31.3 (24.9–32.7)	0	0.824
Interval from PPROM to start of labor (days)	3.8 (1.8–9.2)	0	3.1 (2.0–5.3)	0	0.324
Induction of labor or cesarean section before start of labor	34.0%	0	56.5%	0	**0.026***
Diabetes[c]	3.8%	0	13.0%	0	**0.029***
Hypertension[c]	1.2%	0	0.0%	0	0.604
Preeclampsia	0.7%	0	4.4%	0	0.051
Lag time from the last corticosteroid administration to start of labor (hours)	82 (29–230)	0	51 (30–168)	0	0.422
Number of CTG traces (30 minutes) before start of labor	11 (6–19)	0	13 (9–21)	0	0.190
Neonatal characteristics					
Gestational age at birth (weeks)	32.0 (29.4–33.1)	0	31.6 (25.3–33.4)	0	0.394
Birthweight (grams)	1762 (1331–2123)	9	1684 (821–2215)	0	0.522
Female gender	44.5%	0	30.4%	0	0.183
Small for gestational age[d]	9.8%	0	4.4%	0	0.387
pH in umbilical artery at birth	7.31 (7.25–7.36)	227	7.25 (7.22–7.35)	11	0.351
Base deficit in umbilical artery at birth (mmol/L)	2.5 (0.9–4.9)	236	4.5 (1.3–6.1)	11	0.240
Apgar scores at 1 minute	8 (6–9)	11	6 (4–9)	0	**0.004***
Apgar scores at 5 minutes	9 (8–10)	12	8 (6–9)	0	**0.018***
Apgar scores at 10 minutes	10 (9–10)	13	10 (8–10)	0	0.628
Neonatal death within 28 days from birth	1.2%	0	0.0%	0	0.604

*Indicates $p<0.05$.
Abbreviations. PPROM, preterm prelabor rupture of membranes; CTG, cardiotocography.
[a]Mann-Whitney U test and Pearsons Chi^2-test were used where appropriate.
[b]Registered at first visit to maternity care.
[c]Existing before pregnancy or diagnosed during pregnancy.
[d]Defined as birth weight below 2 standard deviations from mean birth weight at current gestational age.

might affect the risk for our proxy EONS, and that they have been shown to affect baseline frequency [44].

Model estimates were accompanied by 95% confidence intervals and p-values, derived from the t-distribution. A P value < 0.05 was considered statistically significant. All statistical analyses were run with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The study was reviewed and approved by the Swedish Ethical Review Authority on March 8, 2017 (2017/323-31), with the approval of additions on June 16, 2019 (2019-03026) and June 25, 2020 (2020-02197). Requirement for consent was waived by the review authority since this is a historical cohort study where all data is deidentified and the results are only presented in aggregated form.

Results

A total of 922 women fulfilled the inclusion criteria. We excluded 186 women who had PPROM < 12 h before giving birth and 58 women because of other reasons (Figure 1), leaving 678 women for analyses of their CTGs with a total of 10 600 CTG traces. Fifty women had only one available CTG trace after PPROM and before the start of labor, which led to exclusion. A total of 43 CTG traces were excluded due to baseline frequency below 110 bpm or STV values > 30 ms, but this did not result in exclusion of any patient, since all of these had other traces within limits. The final study population therefore included 628 women with a total of 9 690 CTG traces.

The demographic and clinical characteristics of the study population are shown in Table 1. There were significantly more women with diabetes in the IAI group (13.0% vs 3.8%, $p=0.029$), and fetuses exposed to IAI had lower 1-min and 5-min Apgar scores after birth than those not exposed (6 vs 8 [$p=0.004$] and 8 vs 9 [$p=0.018$], respectively).

Short-term variation declined steeper in the IAI exposed group in the last 24 h before the start of labor, than in the group without IAI (Figure 2). The decline started 20 h before the start of labor, regardless of whether the labor started spontaneously or not. As shown in Table 2, fetuses exposed to IAI had a 26.5% steeper decline in their STV during these last 24 h when

Table 2. Longitudinal change in short-term variation (STV) per 24 h for fetuses non-exposed and exposed to intraamniotic infection (IAI), with early-onset neonatal sepsis as a proxy for IAI, and a comparison of the two groups. The relative difference in percentage and 95% confidence intervals are shown.

	Hours before start of labor	Longitudinal change in STV (%) per 24 h for IAI cases (95% CI)	Longitudinal change in STV (%) per 24 h for non-IAI cases (95% CI)	Longitudinal change in STV (%) per 24 h for IAI cases *beyond* non-IAI cases (95% CI)	*p* value
Crude	24–168	1.4 (−1.2–4.0)	–	1.4 (−1.2–4.0)	0.302
Adjusted for betapred	24–168	1.4 (−1.1–4.0)	–	1.4 (−1.1–4.0)	0.282
Adjusted for betapred and baseline frequency	24–168	0.7 (−1.5–2.9)	–	0.7 (−1.5–2.9)	0.536
Crude	0–24	−37.3 (−42.7 to −31.3)	−14.6 (−16.1 to −13.2)	−26.5 (−32.9 to −19.4)	**<0.001***
Adjusted for betapred	0–24	−34.6 (−40.3 to −28.5)	−13.6 (−15.1 to −12.2)	−24.3 (−30.9 to −17.1)	**<0.001***
Adjusted for betapred and baseline frequency	0–24	−17.8 (−24.0 to −11.2)	−5.9 (−7.3 to −4.5)	−12.7 (−19.3 to −5.5)	**<0.001***

*Indicates $p < 0.05$.

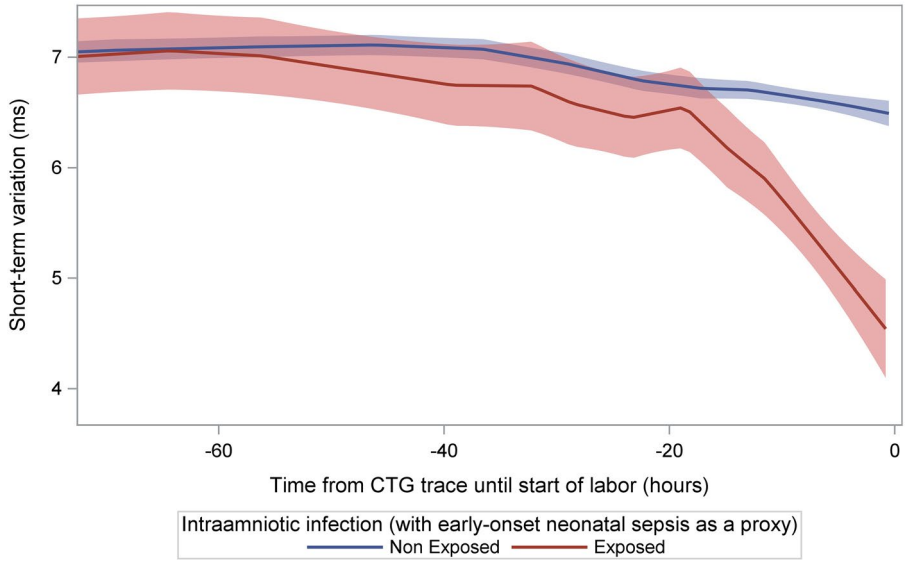

Figure 2. Mean short-term variation during the last 72 h before start of labor, shown with locally estimated scatterplot smoothing curves.

compared to fetuses not exposed (95% CI −32.9% to −19.4%; $p < 0.001$). After adjustment for antenatal corticosteroids, the difference remained significant (−24.3% [95% CI −30.9% to −17.1%], $p < 0.001$). The difference between groups became less prominent after adjustment for the baseline frequency but remained significant (−12.7% [95% CI −19.3% to −5.5%], $p < 0.001$). Before 24 h (24 to 168 h before start of labor), there was no difference in decline between the groups.

As shown in Figure 3, baseline frequency started to increase 12 h before start of labor. Baseline frequency increased by 11.1 bpm in the last 12 h before start of labor in the group exposed to IAI beyond those who were not exposed (95% CI 8.3 bpm to 13.8 bpm; $p < 0.001$). The difference remained unchanged after adjustment for the administration antenatal corticosteroids (Table 3).

Stratifying the study population in two groups by gestational age ≥ 30 weeks and < 30 weeks resulted in similar results, although in the group with gestational age < 30 weeks the results did not remain significant after adjustment for baseline frequency (Supplementary Table S1).

Discussion

In this study, we have shown that in IAI exposed fetuses, STV decreases significantly steeper during the last 24 h before birth than it does in non-exposed fetuses. The increase in baseline frequency explained a part of the effect on STV, but the STV started to decrease hours before baseline frequency started to increase. A decreasing STV can therefore be a signal indicating an intraamniotic infection that is affecting the fetus.

To our knowledge, only one study has previously examined longitudinal change in STV during the PPROM latency period in relation to IAI. In 2017, Vandenbroucke et al. [45] published a retrospective study that included 23 women with PPROM. An STV

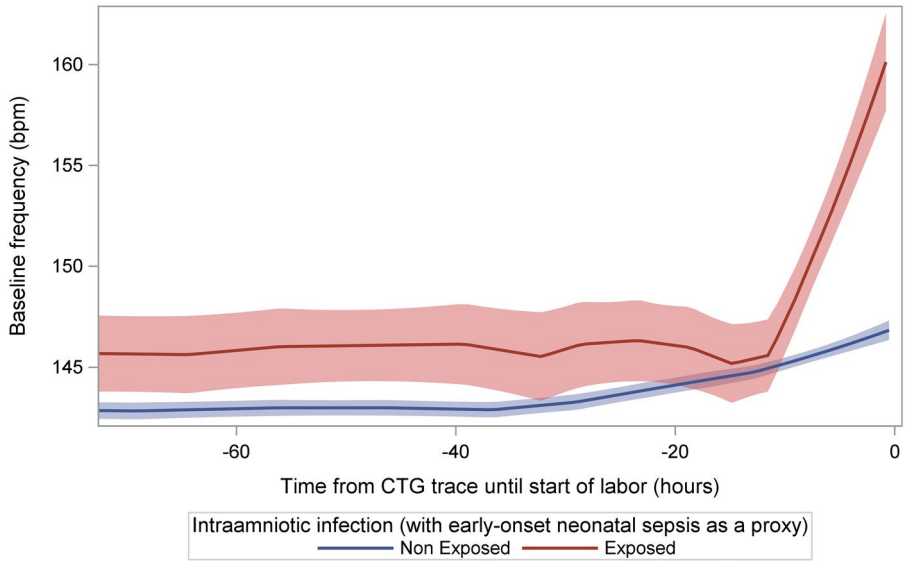

Figure 3. Mean baseline frequency during the last 72 h before start of labor, shown with locally estimated scatterplot smoothing curves.

Table 3. Longitudinal change in baseline frequency (BF) per 12 h for fetuses non-exposed and exposed to intraamniotic infection (IAI), with early-onset neonatal sepsis as a proxy for IAI, and a comparison of the two groups. The absolute difference in beats per minute (bpm) and 95% confidence intervals are shown.

	Hours before start of labor	Longitudinal change in BF (bpm) per 12 h for IAI cases (95% CI)	Longitudinal change in BF (bpm) per 12 h for non-IAI cases	Longitudinal change in BF (bpm) per 12 h for IAI cases *beyond* non-IAI cases	*p* value
Crude	12–168	−0.1 (−0.4–0.3)	–	−0.1 (−0.4–0.3)	0.713
Adjusted for betapred	12–168	−0.1 (−0.4–0.2)	–	−0.1 (−0.4–0.2)	0.639
Crude	0–12	15.7 (13.0–18.4)	4.7 (4.1–5.2)	11.1 (8.3–13.8)	**<0.001***
Adjusted for betapred	0–12	15.5 (12.8–18.1)	4.6 (4.1–5.1)	10.9 (8.1–13.6)	**<0.001***

*Indicates $p < 0.05$.

temporal index was calculated, dividing the mean value of the last two traces before delivery by the mean value of the preceding traces. The temporal index was lower in women with histological chorioamnionitis than in those without (0.7 vs 1.1, $p = 0.003$), implying a decreasing STV with inflammation and/or infection, which is in line with our results.

A few other studies have been performed on the general effect of IAI on STV, but their results have been contradictory. In a case-control study by Day et al. on 36 fetuses, they found no significant differences in the CTGs of those fetuses later developing EONS, compared to those who did not [46]. Meanwhile, a prospective study on 87 women by Buhimschi et al. found that non-reassuring CTG (recurrent late decelerations, severe variable decelerations, prolonged decelerations and fetal bradycardia with absent variability) at admission was significantly more common in fetuses who later developed EONS than in those who did not (35% vs 5%, $p < 0.001$) [47]. These two studies were small in size. As previously mentioned, our research group recently published a cohort study on 678 women with PPROM, showing a 20.5% lower STV in the last CTG trace before delivery among those with IAI compared to those without. With the current study, we have added further knowledge on the longitudinal change in STV during the PPROM latency period.

Other factors known to affect STV are maternal diabetes, maternal smoking, fetal tachycardia, fetal sleep and medications such as corticosteroids [48–51]. STV is also known to increase with increasing gestational age. In the current study, the population was too small to detect differences in STV after adjustment in the group with gestational length below 30 weeks. Another factor known to be correlated to decreased STV is metabolic acidemia [52]. The association between IAI and decreasing STV in the current study is, in our belief, not caused by acidemia. Through activation of the cholinergic anti-inflammatory pathway, infection leads to vagal nerve activation, affecting the heart rate variation. Infection also leads to an increase in proinflammatory

cytokines that depress the heart rate variation and directly affect the sinoatrial node pacemaker cells [53]. Studies on neonates have shown that decreased heart rate variation occurs early in the course of sepsis, often before clinical signs of illness. Our belief that the shown longitudinal decrease in STV is associated with IAI and not with acidemia is further supported by umbilical cord blood gas analyses as shown in Table 1.

The strength of the current study is the size of the study population, which is much larger than in previous studies on the association between STV and IAI. The results of the study are also strengthened by the focused adjustments made for confounders. We consider the generalizability of the study to be good since we included the entire Stockholm County, including all municipalities and delivery units. In Stockholm County, there are around 30,000 births each year. The choice of EONS as a proxy for IAI is another strength of this study. As previously stated, histological chorioamnionitis has often been used as a proxy for IAI, but studies have shown that histological chorioamnionitis has low specificity and sensitivity for both IAI and neonatal outcome, as it can be present in the absence of both positive microbiology and biochemical markers for inflammation. The fact that the prevalence of histological chorioamnionitis is high after a pregnancy complicated by PPROM further diminishes the value of histological chorioamnionitis as a proxy for IAI in the PPROM setting [16–18,22,23]. Therefore, the risk of misclassification bias is substantial when using histological chorioamnionitis as proxy. As IAI and EONS are strongly associated [9,24,25], we consider EONS a better proxy for IAI. One can also speculate the plausibility of a correlation between the degree of severity of an intraamniotic infection and the development of early-onset neonatal sepsis. Monitoring women after PPROM, focusing on detection of IAI and optimal timing for delivery, is a delicate balance between the benefits of prolonging the pregnancy for the fetus and the risk of IAI and its severe consequences. Finding a diagnostic tool suggesting fetal compromise due to IAI, such as sepsis, would be valuable. This further strengthens the choice of EONS as a proxy for IAI.

This study has some limitations. Residual confounding cannot be controlled for in an observational study. Its retrospective nature is another limitation, as variables were not registered for purpose of this study. However, the risk of information bias is low since the variables were registered prospectively during antenatal visits, decreasing the risk of recall bias. There were no missing data on variables used for statistical analyses. A risk of misclassification cannot be excluded, with some infected neonates possibly being falsely grouped as neonates without infection. Preterm neonates often have subtle and nonspecific clinical signs and symptoms of sepsis, as well as a limited ability to produce inflammatory markers. This can result in some cases being undetected by the criteria for neonatal sepsis. If this misclassification is actual, our results might underestimate the difference in longitudinal change in STV when using EONS as a proxy for IAI. The decrease in STV, although significant, is not large, and a decrease of this size can be seen between two consecutive CTG traces in the absence of IAI; as an example, if a fetus is in an active phase during one CTG trace, and in a sleep phase during the next. Therefore, when monitoring a woman for suspected IAI, several CTGs would need to be analyzed, or a continuous CTG for a longer period, to confirm a decrease. Before applying our results into clinical practice, they need to be examined further in a prospective study.

Conclusion

In this study, we have found that STV decreases significantly steeper during the last 24 h before the start of labor in fetuses affected by IAI than in those not affected. The decrease difference remained significant after adjustment for baseline frequency and antenatal corticosteroids. The association between STV and IAI needs to be further studied to evaluate STV's efficacy as a diagnostic tool for IAI when monitoring women after PPROM.

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Author contributions

MH initiated the study. All authors participated in the study design. BTB and MH performed the acquisition of data. FA and KL performed the computerized analyses of CTG traces. BTB performed the statistical analyses in cooperation with TA. All authors participated in the interpretation of data. BTB wrote the first draft of the manuscript, and all authors revised the manuscript and approved the final version for submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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