Heart Rate Analysis to Identify At-Risk Fetuses for Hypoxic-Ischemic Encephalopathy during Fever

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Abstract

Background: *During labour, severe, prolonged, or frequent hypoxia can lead to hypoxic-ischemic encephalopathy (HIE), potentially causing brain injury or death.*

Objective: *Investigate how maternal fever affects fetal heart rate (FHR) in labour and its association with HIE.*

Methods: *We analysed maternal temperature and FHR data from a retrospective cohort of singleton infants ($\geq$35 weeks) delivered at 15 Northern California Kaiser Permanente hospitals (2011–2019). PeriGen Patterns was used to obtain FHR patterns (baseline, decelerations, accelerations). Outcomes were classified into four groups based on umbilical cord or early infant blood gas and neurological exams: (1) HIE, (2) Acidosis Alone, (3) Healthy, No Acidosis, (4) Presumed Healthy. Data were stratified by the presence of intrapartum fever ($\geq$38°C). A linear mixed-effect model was used to model the relationship between FHR and maternal temperature, adjusting for labour progress, epidural use, hospital site, and pregnancy.*

Results & Conclusion: *In the fever group, all outcome classes showed significant increases in baseline FHR and deceleration time compared to before fever. Differences in baseline FHR between the HIE and Healthy outcome classes increased for higher temperatures. These findings highlight the need to consider fever status when developing clinical guidelines or models based on FHR data.*

1. Introduction

During labour, severe, prolonged, or frequent fetal hypoxia can lead to hypoxic-ischemic encephalopathy (HIE), a form of newborn brain injury [1]. In total, HIE affects 1.3-1.7 [2] and 1.5-26.5 [2–4] per 1,000 live births in developed and developing countries, respectively. It is a major cause of long-term neurodevelopmental issues[1, 4–6], death in the first month of life [3, 4], and medical malpractice claims [5, 6]. There is a need for the timely detection of hypoxia and risk assessment to identify fetuses that are more susceptible and less tolerant to hypoxia.

Two important indicators of fetal stress during labour are maternal fever and fetal heart rate (FHR). Maternal fever, defined as a body temperature greater than 38°C, is typically caused by maternal infection and/or epidural administration [7]. In animal models, it is associated with decreased tolerance of the fetus to labour and hypoxia [8]. More recently, it has been shown that both higher maximum maternal temperature and earlier onset of fever in labour are associated with a higher risk for HIE [9].

FHR, along with uterine pressure (UP), is typically measured with cardiotocography (CTG). In clinical guidelines [10] and novel automated decision support software [11], FHR patterns (baseline, decelerations, accelerations) are used to assess fetal well-being.

The objective of this study is to examine how maternal fever affects FHR features during labour, and whether this modifies the association with HIE.

2. Dataset

CTG records and maternal vital signs linked to information about the infant, mother, pregnancy, labour, and outcome were obtained from a retrospective cohort delivered at 15 Northern California Kaiser Permanente Hospitals between 2011-2019, amounting to over 250,000 births [12].

The outcome label of HIE was defined as a combination of acidosis (indicating hypoxia) and encephalopathy (indicating brain dysfunction). Acidosis was determined based on blood gas assessment; at least one pH$<$7 or base deficit $\geq$10 mmol/L from any cord blood, or a base deficit $\geq$10 mmol/L on the first infant blood gas before 2 hours of age. Encephalopathy was defined as at least one of the following: abnormal neurological exam lasting $\geq$6 hours, seizures in the first 24 hours of life, or received therapeu-

tic hypothermia. Exclusion criteria were stillbirths, death $\leq$ 6 hours after birth, and neonates with congenital abnormalities or without acidosis that required intervention at birth. Overall, four outcome groups were classified: (1) HIE, (2) Acidosis alone, (3) Healthy, no acidosis, (4) Presumed healthy, no blood gas assessment [12].

Inclusion criteria were singleton, cephalic presentation pregnancies with a gestational age $\geq$35 wks, delivered either vaginally or had an unscheduled caesarean section.

2.1. FHR Processing

PeriCALM Patterns, a software system developed by PeriGen Inc., was used to preprocess the FHR. FHR was sampled at 4 Hz. PeriCALM Patterns identified signal gaps and segments contaminated with high levels of noise. Signal gaps shorter than 15 s were interpolated using linear interpolation [13, 14]. Signal gaps longer than 15 s and noisy segments were labelled as uninterpretable.

After preprocessing, PeriCALM Patterns used a long-short-term memory network to identify the location and duration of CTG events, namely, FHR baselines, accelerations and decelerations [13, 14].

FHR signals were then divided into non-overlapping 20-minute epochs. We computed the following FHR features for each epoch: (1) mean baseline FHR, (2) total acceleration duration, and (3) total deceleration duration. For epochs with >20% of samples missing or uninterpretable, the FHR features were set to NaN to mark them as invalid.

2.2. Maternal Temperature and Cervical Dilation

Maternal temperature and cervical dilation records were interpolated in a feed-forward manner to achieve a one-minute time resolution. Maximum temperature and last dilation record per epoch were then calculated.

The intrapartum (labour) period was defined as records within 72 hours before birth. Data were stratified by the presence of intrapartum maternal fever ($\geq$38°C). Data breakdown is presented in Table 1.

Table 1: Dataset Breakdown

Group	Fever	No Fever
HIE	120	227
Acidosis Alone	709	2,218
Healthy, No Acidosis	5,564	30,244
Presumed Healthy	9,458	139,163

3. Fever Onset and FHR Features

The first epoch occurrence of $\geq$38°C was recorded as the fever onset time $t_0 = 0$. Epoch timings were then referenced to t_0. Figure 1 shows mean baseline FHR, total deceleration duration, and total acceleration duration with respect to t_0.

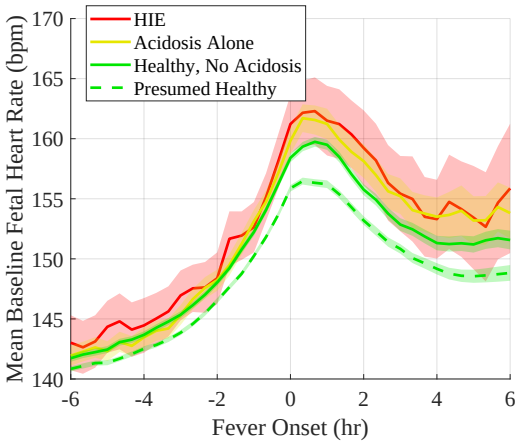
4. Adjusted Relationship of FHR with Maternal Temperature

In addition to examining the fever subgroup, we examined the relationship between maternal temperature and FHR features for all epochs. As FHR features and maternal temperature are time-varying, correlated for the same pregnancy and hospital site due to similar data acquisition and clinical processes, and affected by epidural administration, these factors need to be adjusted for.

A linear mixed-effects model was used to model the relationship between FHR and maternal temperature for the different outcome groups. The model was chosen for its ability to correct for both fixed and random effects. Fixed-effects terms are the conventional predictors/confounders in regression analysis that are assumed to be constant across individuals. Random effects allow for variability between different clusters, which can be hierarchical in nature. That is, multiple recordings from a patient, and multiple patients from a hospital. It is assumed that the clusters are related by an underlying distribution, whereas fixed effects are not. Hence, mixed-effects models are suitable for dealing with multiple measurements over time for the same pregnancy. Additionally, mixed-effects models are capable of dealing with missing outcome data.

Fixed effects adjusted for were labour progress (measured by cervical dilation), epidural administration, and their interaction with maternal temperature. Random effects adjusted were hospital site and pregnancies. The hospital site was adjusted using random intercepts, and individual pregnancies were adjusted with random slopes and intercepts. The overall model is present in Equation 1, and the resultant fitted models are presented in Figure 2.

$$\begin{aligned} FHR\ Feature \sim\ & Maternal\ Temperature + Cervical \\ & Dilation + Epidural\ Administration + \\ & (Maternal\ Temperature : Cervical\ Dilation) + \\ & (Maternal\ Temperature : Epidural\ Administration) \\ & + (Maternal\ Temperature : Outcome\ Group) + \\ & Outcome\ Group + (1|HospitalSite) + \\ & (1 + Cervical\ Dilation|Pregnancy\ ID) \end{aligned} \quad (1)$$



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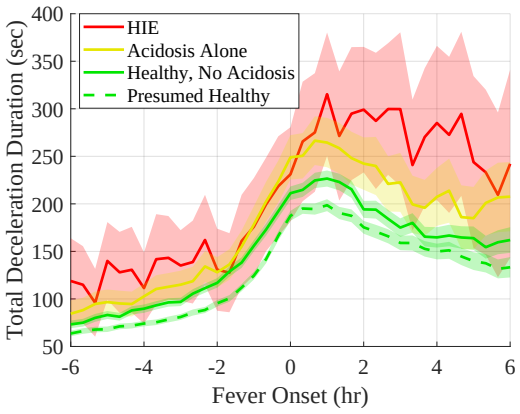

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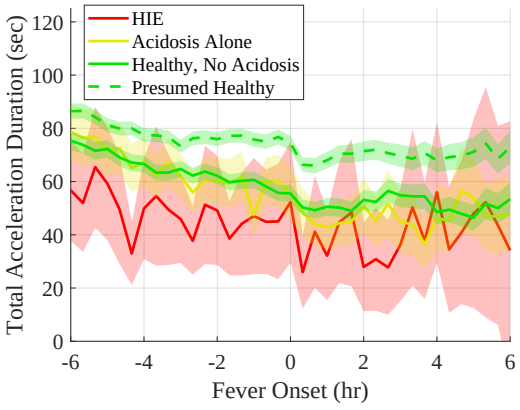
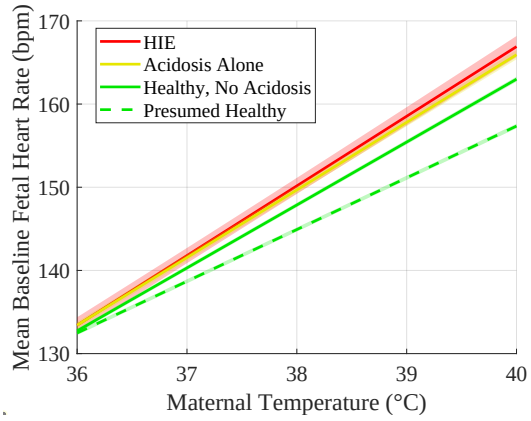


(c)

Figure 1: Fever Onset Time vs Fetal Heart Rate Features. Line= Mean Feature Value. Shaded Region= 95% Confidence Interval.



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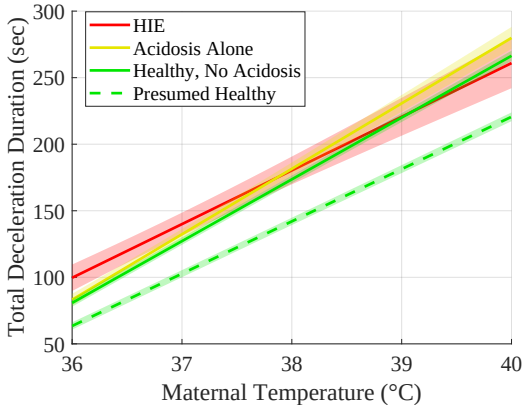

(b)

Figure 2: Population Average Maternal Temperature vs Fetal Heart Rate Features. Fitted Linear Mixed Effects Model with Epidural Administered= True and Cervical Dilation = 6 cm. Line= Model Prediction. Shaded Region= 95% Confidence Interval.

5. Results and Discussion

In the fever group, all outcome groups showed statistically significant increases in mean FHR baseline (Figure 1a) and total deceleration duration (Figure 1b). These changes begin several hours earlier than the initial detection of fever onset and persist once fever occurs. While the peak temperature is typically observed at fever onset, peak mean baseline FHR and total deceleration duration are observed in the subsequent hour. In contrast, the total acceleration duration was consistently decreasing irrespective of fever onset time (Figure 1c).

The presence of fever is a known risk factor for HIE (unadjusted relative risk = 5.73), however, maternal temperature is irregularly recorded. Hence, the mean baseline FHR and total deceleration duration may provide earlier indicators of fever. This is shown by the large increases

several hours before the initial detection of fever onset. Once fever onset occurs and in the subsequent hours, there is a larger difference between outcome groups. That is, while all outcome groups show an increase in feature values, poorer outcome groups show larger increases. This suggests the need to consider fever status when defining clinical guideline thresholds or developing machine learning models based on FHR data.

As shown in our previous work [9], HIE is associated with higher maximal maternal temperatures and earlier fever onsets. As the mean baseline FHR and total deceleration duration are associated with maternal temperature and labour timing, the question arises whether Figure 1 differences in outcome groups are due to different distributions in maternal temperature and labour timing or different responses to maternal temperature.

Figure 2 shows the adjusted relationship between FHR features and maternal temperature. For total deceleration duration (Figure 2b), the slopes between the outcome groups are similar, whereas the intercepts differ. This suggests that whilst total deceleration duration is an indicator of fetal distress, its relationship with maternal temperature is similar between outcome groups. On the other hand, for the mean baseline FHR (Figure 2a), the worse the outcome class, the larger the slope between maternal temperature and baseline FHR. This suggests that fetuses that develop HIE have a lower tolerance to temperature increases.

6. Conclusion

Maternal fever during labour is a known risk factor for HIE. The observed changes in baseline FHR and deceleration duration suggest increased physiological stress, supporting this association. These features also show significant increases before fever onset that persist post-onset.

For the mean baseline FHR, the response to maternal temperature differs by outcome group: fetuses that develop HIE are less tolerant to maternal temperature increases.

Overall, these findings highlight the need to consider fever status and potentially maternal temperature directly when defining clinical guideline thresholds or developing machine learning models based on FHR data.

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