Longitudinal Assessment of Fetal Heart Rate Variability During Pregnancy

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Abstract

Inadequate development of the fetal autonomic nervous system (ANS) during gestation can lead to health problems not only in the perinatal period but well into adulthood. Assessing fetal heart rate variability (fHRV) may allow for tracking fetal autonomic development and identification of abnormalities. A HRV methodology which is well-suited to this purpose is phase rectified signal averaging (PRSA). While PRSA has been used in assessing autonomic dysfunction related to complications such as fetal growth restriction, knowledge on how PRSA features change with gestational age is limited. In this paper, we use PRSA to analyze a dataset comprising of repeated abdominal ECG measurements acquired throughout healthy pregnancy (29 participants, 184 recordings) to capture how PRSA features evolve over the second half of gestation. Results show that all features change significantly ($p < 0.01$), typically increasing from 22 to around 31 weeks (likely due to quicker signaling between nerve cells, corresponding to the rapidly maturing parasympathetic nervous system) and then stabilizing or slightly decreasing thereafter owing to better control of the heart rate by the mature fetal ANS. We conclude that PRSA features change with progressing gestation and may be a useful tool for tracking the maturation of the fetal ANS.

1. Introduction

Healthy development of the autonomic nervous system (ANS) is essential to a person's well-being. As early as during the gestational period, abnormal autonomic activity is associated with fetal abnormalities such as fetal growth restriction (FGR) [1]. Furthermore, impaired autonomic development can have lifelong consequences; ANS immaturity due to perinatal complications such as preterm birth can lead to impaired behavior, stress response, and mood regulation in adulthood [2]. Subsequently, detecting impaired fetal autonomic development would provide information to clinicians to support decision-making and allow for planning appropriate interventions where possible.

A proxy measure for autonomic regulation is fetal heart rate variability (fHRV), which is used to assess fetal well-being and may be useful in tracking fetal neurodevelopment [3,4]. Further compounding the potential to track fetal development is the increasing availability of wearable fetal HR monitors which record the information needed to calculate fHRV.

However, as poor data quality often impedes fHRV analyses [4], the use of HRV methodologies that are more robust to noise and missing data would be better suited to long-term fHRV monitoring. One such methodology which has been gaining interest in this domain is phase rectified signal averaging (PRSA), which graphically shows the rate and magnitude of heart rate (HR) decelerations and accelerations [5]. This HRV methodology has been used in identifying fetal complications such as acidemia and fetal growth restriction [1,6], as well as capturing the effect of gestational diabetes mellitus and the administration of betamethasone, a medication commonly given to women at risk for preterm birth, on the fetus [7,8].

Still, it is largely unknown how gestational age (GA) affects PRSA, limiting its clinical interpretation. As the fetal sympathetic and parasympathetic nervous systems (SNS and PNS) are continuously developing throughout gestation, changes may occur in fHRV as pregnancy progresses. Therefore, in this work, we investigate how PRSA changes with healthy fetal autonomic development.

2. Methods

2.1. Dataset

This paper details a secondary analysis of data collected for a previous study [4]. The institutional review board at the Máxima Medical Center, Veldhoven, the Netherlands issued a waiver for this analysis (reference number N21.008). A brief description of the dataset is given here

with further details available in the publication outlining results from the original study [4].

Repeated abdominal ECG measurements were acquired from 40 healthy, singleton pregnancies at 1000 Hz using a non-invasive electrophysiologic monitor (the NEMO device, Maastricht Instruments, the Netherlands). Measurements were done at approximately 14, 18, 22, 24, 26, 30, 34, 36, 38, and 40 weeks of gestation while participants were lying in a semi-recumbent position. Recordings of approximately 45 minutes in duration were done between 08:00 and 18:00. Subjects with missing recordings (n = 4) or who developed complications (n = 7) were excluded, resulting in an eventual analysis of 29 participants. The pregnant women were 31 ± 4 years old, gave birth at 40 weeks ± 10 days of gestation, and had a BMI of 24 ± 4 kg/m^2 before pregnancy. All pregnancies progressed uneventfully and resulted in the delivery of a healthy infant.

2.2. Preprocessing

Abdominal ECG recordings were filtered with a 4th-order Butterworth bandpass filter (1 to 70 Hz) and a notch filter (50 Hz). Fetal R-peaks were extracted with an algorithm detailed elsewhere [9]. To remove possibly erroneous RR-intervals, any RR-intervals which were outside the range of 0.2–1.3 s (46–300 beats per minute [4]) or differed from the preceding interval by more than 20% were excluded. Preprocessing was done in MATLAB (MathWorks, USA) while further processing was done in Python (PSF, USA).

Some recordings had sections of data loss, and the signals were not of consistent quality throughout the recording. Subsequently, for each participant, the five-minute segment with the highest quality per recording (i.e., lowest amount of missing data and unreliable RR-intervals) was selected for the analysis. If the highest quality segment still had more than 25% removed RR-intervals, the recordings were excluded from the analysis (n = 5). In total, 184 recordings were used for the analysis.

2.3. PRSA

Physiological time-series data are often difficult to analyze given that underlying trends in the data may be obscured by noise and non-stationarities. PRSA is a method designed specifically to identify and elucidate quasi-periodicities in such noisy physiological time-series. A detailed description of the method can be found in the original publication [5]. For the purposes of this paper, we give a brief outline of the method:

Two sets of anchor points (APs) are identified, one set corresponding to each acceleration in the heart rhythm and the other corresponding to each deceleration. Thereafter, a window (length: 2*L*) is identified around each AP, long enough to allow for the visualization of the slowest relevant oscillation related to the AP (in our case, L = 25 RR-intervals). Next, all APs in each set are aligned by their common phase (for example, HR decelerations) and averaged, resulting in a waveform. The averaging of these segments eliminates the noise and non-stationarities present in the heart rhythm, and the result is the underlying quasi-periodicity in the signal in relation to HR accelerations and decelerations, respectively. Quantifying the rate and magnitude of periodicity in the heart rhythm gives an estimate of the responsiveness of the ANS [5].

Three sets of features are calculated to quantify this response. First, the most established features, which are deceleration capacity (DC) and accelerations capacity (AC), are calculated as follows:

$$DC/AC = [X(0) + X(1) - X(-1) - X(-2)]/4, \quad (1)$$

with X representing the resulting waveform from the PRSA analysis and X(0) denoting the RR-value at the AP [5]. Additionally, the maximum response in HR around the AP is determined (the immediate deceleration response (IDR) and immediate acceleration response (IAR)) by calculating the difference between the highest and lowest value in the PRSA waveform within five RR-intervals of the AP. Additionally, the slopes corresponding to these maximum responses are calculated, namely the slope of the deceleration and acceleration responses (SDR and SAR) respectively [10].

2.4. Data and statistical analyses

The data are grouped into seven GA bins for this analysis: less than 22 weeks; 22 to 25 weeks; 25 to 28 weeks; 28 to 31 weeks; 31 to 34 weeks; 34 – 37 weeks; above 37 weeks. Since the data in each group were typically not normally distributed (as assessed with D'Agostino's K-squared test), the Kruskal–Wallis test is used to test whether changes across gestation are statistically significant ($p < 0.01$).

Furthermore, the median and interquartile range of the values are plotted to visualize the potentially dynamic changes in PRSA features across gestation. If large changes between bins were apparent from the visualization, we assessed the differences between the two gestational bins using Mann-Whitney U test and Cohen's U_1. The latter is a nonparametric effects size test where U_1 = 0.15, U_1 = 0.33, and U_1= 0.47 suggest small, medium, and large effect sizes, respectively [11].

3. Results

Figure 1 shows the evolution of the PRSA features across gestation. All features changed significantly with GA: for DC, p = 0.001; for all other features, $p < 0.001$.

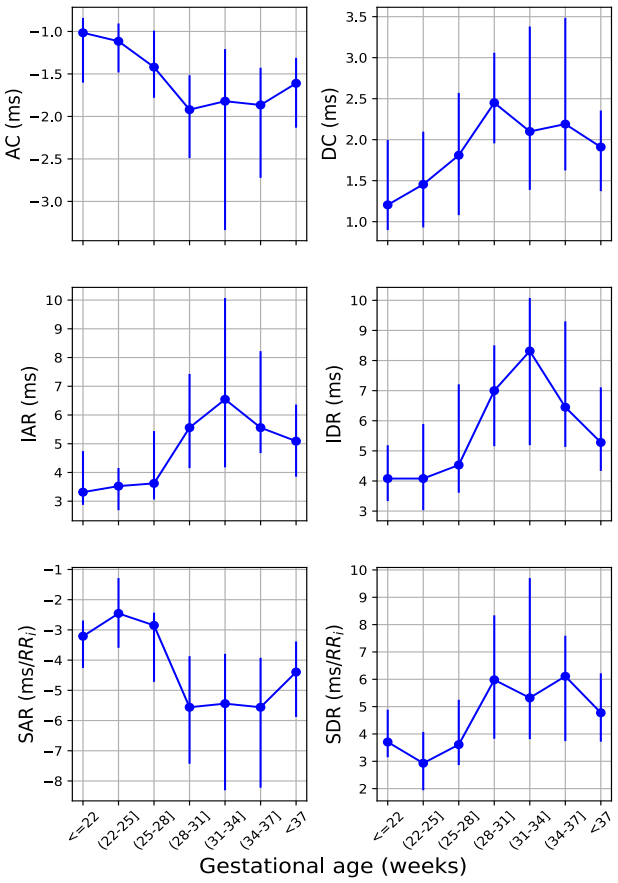

Figure 1: Change in PRSA features plotted against GA bins as median values with interquartile range. From top-left, clockwise: a) AC; b) IAR; c) SAR; d) DC; e) IDR; and f) SDR.

From this visualization (Figure 1) it is apparent that there are potentially large changes in PRSA between approximately 20 to 30 weeks of gestation. Subsequently, we assessed the difference between features from the 22 – 25 weeks of gestation and 28 – 31 weeks of gestation bins (Table 1). The change between bins is significant ($p < 0.01$) for all features, with AC, IDR, and SDR having small to medium effect sizes and IAR and SAR having medium to large effect sizes.

Table 1: Differences in PRSA features between two GA bins, namely 22 to 25 weeks and 28 to 31 weeks. Significance (p-value) and effect sizes (U_1) are reported.

Features	***p*-value**	***U*$_1$**
AC	< 0.001	0.137
DC	0.005	0.098
IAR	< 0.001	0.373
IDR	< 0.001	0.255
SAR	< 0.001	0.392
SDR	< 0.001	0.275

4. Discussion

PRSA is a promising methodology for assessing fetal autonomic regulation. Not only have researchers demonstrated its potential use in identifying fetal complications [1,6] but the robustness of the method to missing data makes it well suited to fetal monitoring, where data quality is often a problem. However, as demonstrated in this paper, it is important to take GA into account when interpreting PRSA features.

Limited work has been done to investigate changes in PRSA with GA. Although Graatsma et al. found that GA had a very limited effect on PRSA features, they observed similar trends in AC and DC: namely, an increase (in absolute terms) leading up to approximately 30 weeks and followed thereafter by a decrease [12]. Furthermore, Stampalija et al. found no differences in AC and DC between 26 to 30 weeks and 30 to 34 weeks of gestation [13]. Neither accounted for fetal behavioral states. When we performed a comparison between these two GA ranges in our data, we similarly found no significant difference in AC and DC.

However, the differences between the 22 to 25 weeks bin and the 28 to 31 weeks bin are significant. While the effect sizes are small in the case of AC and DC, they are medium to large for IAR and SAR. Considering these results as well as the graphs in Figure 1, it is evident that fHRV (as assessed with PRSA) continuously changes as the gestational weeks progress. This also illustrates the potential pitfalls of comparing between gestation groups with a large range, for example comparing fHRV between the second and third trimester, as changes might be missed.

We hypothesize that these apparent changes in the graphs in Figure 1 reflect the maturation of the fetal ANS. From about 25 weeks of gestation, the PNS is starting to rapidly develop until approximately 32 weeks of gestation [2]. In all features, an increase is apparent during this time, suggesting that the heart rhythm can now change more rapidly and with larger fluctuations due to the developing PNS. After 32 weeks, there is a stabilization or decrease in features. This may be a result of the increased vagal control at this stage, as well as a well-developed SNS that changes the HR corresponding to fetal movements [2].

At about 29 weeks, myelination of the vagal nerve occurs [14], which allows for quicker signaling between nerve cells. Interestingly, the sharpest absolute increase can be observed in SAR and SDR at this timepoint, which suggest an increase in the rate of the parasympathetic response echoing the completion of the myelination process.

Still, our analysis is limited. We lack information on the fetal behavior state, which is known to influence fHRV. Since some recordings had poor data quality, we only use 5-min recordings for our analysis, while a PRSA analysis would be strengthened by longer recordings (which translate to more APs.) The length of the signal segments

analyzed (=5 min), further compounds the unknown influence of the fetal behavioral state, since each segment may represent only a single fetal state, while in a longer recording having the presence of different behavioral states may decrease the impact of the limitation.

Yet, despite not stratifying recordings per behavioral state, the dynamic evolution of PRSA features with progressing pregnancy is evident and seems to echo different stages of the development of the fetal ANS. It is also clear that the differences in features between certain points in gestation can be large and GA should be accounted if these features would be used for clinical interpretation. In conclusion, we believe that PRSA analysis is a potentially useful tool for tracking fetal autonomic development.

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