

# The Effects of Advancing Gestation on Maternal Autonomic Response

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## Abstract

*Important changes occur in the maternal autonomic nervous system with advancing gestation. Tracking maternal autonomic modulation with heart rate variability (HRV) may hold opportunities for early detection of pregnancy complications such as hypertensive disorders of pregnancy (HPD) since these are associated with autonomic dysfunction. However, traditional HRV features often show conflicting trends over gestation. In this paper we implement phase rectified signal averaging (PRSA) to longitudinally track autonomic response throughout gestation. Since other fields of investigation have shown attenuated autonomic responsiveness in healthy pregnancy, we hypothesized that assessing PRSA longitudinally over pregnancy would elicit a clearer trajectory of autonomic modulation. We found that autonomic responsiveness becomes significantly attenuated towards the end of pregnancy, although not to a degree that is comparable to diseased states. PRSA features show clear downward trends across pregnancy, with an uptick right before pregnancy ends, perhaps showing increased autonomic activity in preparation for delivery. We conclude that longitudinal analysis using PRSA holds promise as a potential screening tool for high-risk pregnancies.*

## 1. Introduction

Maternal autonomic adaptation is essential in facilitating the physiological changes that a healthy pregnancy necessitates [1], yet the trajectory of this autonomic modulation remains poorly understood [2]. Since pregnancy complications are linked to insufficient autonomic adaptation, mapping the trajectory of healthy autonomic modulation will not only provide clinical insight [3], but could also allow for the early detection of emerging deteriorations in maternal health.

There is particular interest in tracking autonomic activity with heart rate variability (HRV), as HRV can be longitudinally and unobtrusively assessed with wearables. Literature on this topic is focused on HRV features that

capture the activity of the sympathetic and parasympathetic nervous systems, but results remain inconsistent. While most researchers found a shift from parasympathetic to sympathetic dominance with advancing gestation [2], others found no difference across pregnancy [4]. These analyses typically focus on HRV features in the frequency domain, which are known to be sensitive to test setup and noise.

However, there are other characteristics of autonomic modulation that can be exploited for the purposes of tracking autonomic trajectory. It is well documented that there is a blunting in maternal physiological responses with healthily progressing gestation. This phenomenon, which is typically attributed to a blunted autonomic response [5], has been studied in various ways.

Firstly, baroreflex sensitivity is reduced towards the end of pregnancy, suggesting attenuated autonomic control of blood pressure [6]. Secondly, while studies using microneurography to assess maternal autonomic activity found a state of sympathoexcitation, they also observe a reduction in neurocardiovascular transduction [7]. Lastly, there is growing evidence that healthy pregnant women are hyporesponsive to physical, cognitive, and psychological challenges [5]. This is concluded from investigations showing an attenuated response to cardiac reflex-maneuvers, blunted renin response to thermal stress, attenuated pain reception, inadequate cortisol response to cold pressor tests, and lack of response to relaxation techniques [5].

While the techniques used in these investigations are not suitable for long-term, unobtrusive monitoring, there is an approach to HRV analysis that can capture the robustness of autonomic response. Phase rectified signal analysis (PRSA) and its accompanying features capture the responsiveness of HR to decelerations or accelerations and in doing so offers insight into autonomic response. This technique is also more robust to noise than standard HRV analyses. This technique has been used to capture the effects of aging on autonomic activity [8], to predict mortality in cardiac disease [9], and to assess fetal health [10]. The use of PRSA in assessing maternal state is limited to assessing the impact of exercise and pregnancy complications on autonomic response [11,12]. In this

paper, we investigate whether PRSA-approaches capture the blunted autonomic response that is associated with progressing gestation.

## 2. Methods

### 2.1. Dataset

Maternal ECG was derived from fetal ECG measurements (1000 Hz) which were acquired repeatedly from healthy pregnant women with a non-invasive electrophysiologic monitor (the NEMO device, Maastricht Instruments, the Netherlands) at approximately 14, 18, 22, 24, 26, 30, 34, 36, 38, and 40 weeks of gestation. Measurements were performed for 45 minutes between 08:00 and 18:00 while participants were lying comfortably in a semi-recumbent position. Subjects, of whom 29 were included in this analysis, were  $31 \pm 4$  years old, gave birth at 40 weeks  $\pm 10$  days of gestation and had a BMI of  $24 \pm 4$  kg/m<sup>2</sup> before pregnancy. This paper is a secondary analysis of an existing dataset for which a waiver was granted by the institutional review board at the Máxima Medical Center, Veldhoven, the Netherlands (reference number N21.008). Details on the original study can be found here [13].

### 2.2. Preprocessing

A 4<sup>th</sup>-order Butterworth bandpass filter (1 to 70 Hz) and a notch filter (50 Hz) were applied to the fetal ECG recordings. Thereafter, a fixed linear combination was used to enhance the maternal QRS complexes [14], followed by a peak detection algorithm as described in [21], with the relative characteristic frequency of the wavelet set to 19 and the HR limits to 30 and 210 bpm, to extract the maternal tachogram [15]. Possible ectopic beats or motion artifacts were removed by rejecting RR intervals which fell outside a specified range (0.4 to 2 seconds) or differed from the preceding interval by at least 20% [8,16]. Preprocessing was done in MATLAB (MathWorks, USA) and further processing was done in Python (PSF, USA).

### 2.3. PRSA

PRSA is used to identify and elucidate quasi-periodicities in physiological time-series data which are often obscured by noise and non-stationarities [17].

In this paper, we follow four steps to isolate the underlying trend in the tachogram. First, we identify two sets of anchor points (AP), namely all HR accelerations and decelerations. Second, signal segments are isolated by defining a window of length  $2L$  around each AP. These windows should be sufficiently long to capture and visualize the slowest anticipated oscillation of relevance.

We define  $L$  as 50 RR values. Third, all identified signal segments are aligned corresponding to their APs, thereby aligning them by a common phase. Finally, these segments are averaged, visualizing the behavior of HR in response to accelerations and decelerations, respectively. In essence, the magnitude and rate of this response in HR gives an estimate of autonomic responsiveness [17].

To quantify this response, we calculated several features. First, we determine the most prominently used feature, deceleration capacity (DC), as follows:

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

with  $X$  denoting the RR values of the PRSA signal and  $X(0)$  representing the RR value at the AP [17]. Acceleration capacity (AC) is calculated similarly.

Furthermore, the immediate deceleration response (IDR) and immediate acceleration response (IAR) are calculated to capture the maximum response in HR in the immediate neighborhood of the AP. The rate of this maximum response is captured in the slope of the deceleration and acceleration responses (SDR and SAR) respectively. These features are further detailed here [18].

### 2.4. Data and statistical analyses

Data were analyzed with two aims in mind. First, we examined the temporal evolution of PRSA features over gestation. We grouped the features into the following gestational age (GA) bins: 12 to 16 weeks; 16 to 20 weeks; 20 to 24 weeks; 24 to 28 weeks; 28 to 32 weeks; 32 to 36 weeks; and above 36 weeks. Subsequently, we plotted the mean and standard error of the mean (SEM) per bin against GA.

Second, we aimed to capture the statistical significance and magnitude of changes observed. We divided the data into three GA groups to facilitate comparison: less than 23 weeks (GA<sub>1</sub>), between 23 and 32 weeks (GA<sub>2</sub>), and over 32 weeks of gestation (GA<sub>3</sub>). Where participants had multiple measurements per group, we took the mean value of the features calculated from these measurements. We performed a Friedman's test with a Dunn's post hoc test to determine significance of differences between groups. We added Bonferroni correction to control for family-wise error. We considered  $p < 0.05$  to be statistically significant. Corresponding effect sizes were calculated with Cohen's  $U_1$ , which provides a measure of the overlap between the distributions of two groups. A higher  $U_1$  indicates a larger effect size [19].

## 3. Results

Figure 1 shows the temporal evolution of the PRSA features. Notice that all features are decreasing in absolute terms across gestation before showing a slight

Table 1: Results from the grouped analysis for PRSA features. All continuous data are presented as median (IQR).

Features	GA1	GA2	GA3	Friedman p-value	GA1→GA2		GA2→GA3		GA1→GA3	
	median (IQR)	median (IQR)	median (IQR)		p	$U_1$	p	$U_1$	p	$U_1$
AC (ms)	12.5 (8.3 – 17.3)	9.7 (5.9 – 13.0)	8.2 (6.1 – 11.2)	<b>&lt;0.0001</b>	0.221	0.071	1	0.036	<b>0.021</b>	0.107
IAR (ms)	28.9 (19.7 – 43.2)	24.0 (15.8 – 30.3)	19.6 (16.5 – 26.7)	<b>&lt;0.0001</b>	0.256	0.089	1	0.071	<b>0.027</b>	0.179
SAR (ms/RR <sub>i</sub> )	-17.3 (-27.1 – -12.3)	-11.7 (-16.0 – -6.8)	-7.2 (-10.1 – -4.4)	<b>&lt;0.0001</b>	<b>0.037</b>	0.054	0.209	0.036	<b>&lt;0.0001</b>	0.125
DC (ms)	11.7 (8.3 – 14.9)	9.5 (5.8 – 12.8)	8.4 (6.2 – 11.7)	<b>0.002</b>	0.533	0.054	1	0.018	0.176	0.036
IDR (ms)	27.1 (18.6 – 39.7)	23.3 (16.2 – 30.5)	20.8 (16.0 – 27.9)	<b>0.007</b>	0.600	0.036	1	0.018	0.228	0.071
SDR (ms/RR <sub>i</sub> )	15.8 (11.6 – 29.3)	11.9 (7.1 – 16.0)	7.2 (5.6 – 11.5)	<b>&lt;0.0001</b>	0.053	0.089	0.242	0.034	<b>0.0001</b>	0.143

IQR = interquartile range, GA = gestational age

uptick right before the end of pregnancy. This is reflected in Figure 2, which graphically demonstrates the blunting in HR responsivity as evidenced by the reduction in the magnitude of the response between GA<sub>1</sub> and GA<sub>3</sub>. From Table 1, we can see that all features decrease significantly over pregnancy. However, effect sizes are relatively small, with IAR having the largest value ( $U_1=0.18$ )

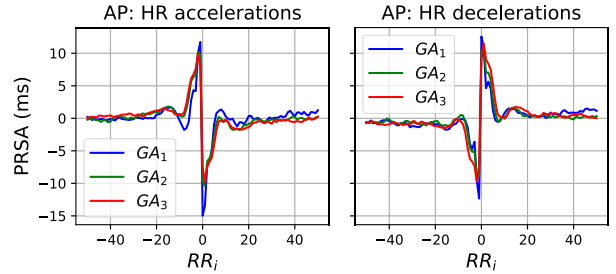


Figure 2: PRSA curves for each GA group with a) accelerations as AP and b) decelerations as AP. In all cases, the mean values have been subtracted from the graphs to enable comparison.

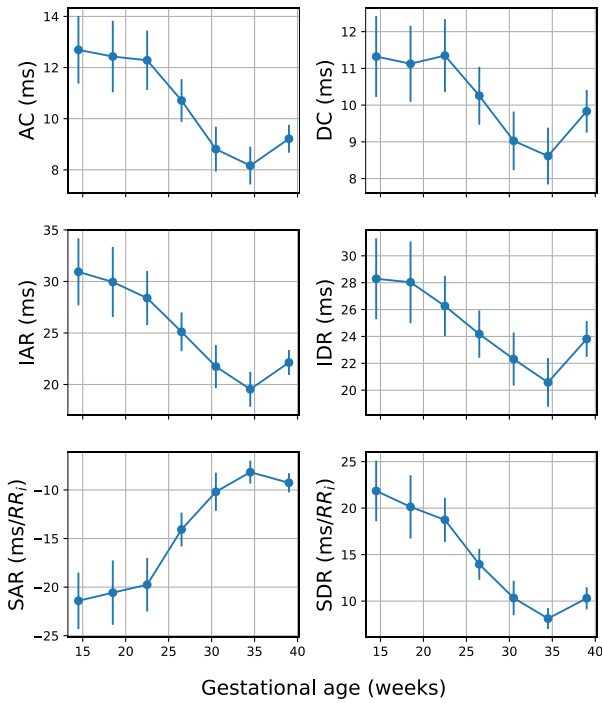


Figure 1: Temporal evolution of PRSA features over GA. HRV features for all participants were grouped into bins of four weeks. The mean and standard error of the mean of the HRV features per bin is plotted against GA. a) AC; b) IAR; c) SAR; d) DC; e) IDR; and f) SDR.

## 4. Discussion

In this study, we implemented PRSA analyses to track autonomic modulation across healthily progressing pregnancy. We hypothesized that in doing so we would capture a blunting in maternal autonomic response [5]. As expected, we observed a significant reduction in PRSA features which capture the magnitude and rate of the autonomic response across gestation.

Our analysis shows that we can map a clear trajectory of maternal autonomic modulation using HRV analyses (Figure 1). Furthermore, in their PRSA analysis of healthy and complicated pregnancies, Casati et al. found that women with complicated pregnancies had significantly higher DC values than healthy ones [11]. While longitudinal PRSA analyses of complicated pregnancies are needed to confirm, it does seem that PRSA is a promising tool for screening high-risk pregnancies. It could be particularly useful if the downward trend in IAR and IDR (Figure 1c and d) emerges before 20 weeks of gestation, since HPD are officially only diagnosed after this GA. The uptick in all PRSA features right before birth is also interesting and warrants further investigation into whether this change in trend occurs before premature deliveries as well. If that is so, this uptick indicates an increase in autonomic responsiveness in preparation for delivery and may serve

as a tool for predictive monitoring.

The reason for this attenuation in autonomic response in healthy pregnancies remains unclear. Even though the reductions in PRSA features are significant, they are not comparable to the changes observed in disease states [9]. One might argue that a blunted autonomic response contributes to the increased susceptibility of pregnant women to infection [20]. The interaction of the neuro-immune axis is well documented and the maternal immune system is known to undergo modulation to support the fetus. However, since reproductive physiology typically evolves to ensure the survival of a species, it seems more likely that this blunted autonomic response serves a protective purpose. DiPietro et al. argue that this attenuated response serves as a buffer between maternal stress and the fetus to create a stable intrauterine environment [5]. Moreover, it could also protect the mother. In cases of cardiovascular disease, an overactive sympathetic system is harmful, even deadly, while high parasympathetic activity has a protective effect [21].

Since healthy pregnancy seems to necessitate high sympathetic activity with suppressed vagal influence, this blunted autonomic response – especially considering the attenuated neurocardiovascular transduction seen in pregnancy – may serve to protect the mother against this altered autonomic state. The cause behind the attenuation of the autonomic response is also not known, but several studies have indicated that estrogen (which increases during pregnancy) dampens autonomic responses [5].

Although the results of our investigation are promising, an investigation with a larger sample size that includes complicated pregnancies is necessary to establish the potential of longitudinal PRSA as a screening tool for high-risk pregnancies.

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