

Autonomic Cardiovascular Control in Pregnancies With Abnormal Uterine Perfusion

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Background: Abnormal uterine perfusion is associated with the development of hypertensive pregnancy disorders. However, its impact on maternal autonomic cardiovascular control is poorly understood. The aim of our study was to investigate the adaptation of autonomic control during pregnancy with abnormal uterine perfusion with normal and pathologic outcome in comparison to normal pregnancies, based on blood pressure variability (BPV), baroreflex sensitivity (BRS), and heart rate variability (HRV) analyses.

Methods: A total of 32 healthy pregnant women (CON, age 28 years, range 24 to 31 years); 16 women with abnormal uterine perfusion and normal outcome (AP-NO, age 29 years, range 28 to 33 years); and 19 women with abnormal uterine perfusion and pathologic outcome (AP-PO, age 26 years, range 25 to 30 years), were recruited for this longitudinal study. Beginning in the 20th week of pregnancy, the women were monitored every fourth week until delivery. For the analysis of BPV, BRS, and HRV, high-resolution ECG, and noninvasive continuous blood pressure (BP) recordings were taken simultaneously for 30 minutes.

Results: CON showed pregnancy-induced adaptation of cardiovascular control; in the course of gestation BPV was increased while parameters of HRV and BRS were reduced. On the contrary, no changes during the second half of pregnancy could be observed in pregnancies with abnormal perfusion. Variability parameters were significantly altered in women with abnormal perfusion compared with CON, whereas these changes were more pronounced in AP-PO compared with AP-NO.

Conclusions: Abnormal uterine perfusion, independently of the pregnancy outcome, has a significant impact on maternal cardiovascular control. Measures of BPV, BRS and HRV might be used for improved risk stratification. Am J Hypertens 2006;19:306–312 © 2006 American Journal of Hypertension, Ltd.

Key Words: Heart rate variability, BP variability, baroreflex sensitivity, normotensive pregnancy, reduced uterine perfusion, cardiovascular control, preeclampsia, intrauterine growth restriction.

Preeclampsia is a major cause of maternal and fetal mortality and morbidity, affecting about 3% of pregnant women. It accounts for a very low birth weight (<1500 g) in 25% of all babies and occurs in approximately 100,000 cases in the United States.¹ The etiology of preeclampsia is complex and not well understood in detail. However, the commonly accepted opinion confirms a disturbed trophoblast invasion in the spiral arteries.² As a consequence of an endothelial dysfunction the uterine perfusion is reduced. Uterine arterial perfusion measured via Doppler blood flow waveforms is currently used as a risk predictor for preeclampsia. However, the positive predicting accuracy is only 20%³ and the causal

link between reduced uterine blood flow, placental pathology, and pregnancy complications is not as strong as once thought.^{4,5} There is obviously a large range of variation in terms of pathologic placental alterations in both normal and complicated pregnancies.

Blood pressure variability (BPV) and heart rate variability (HRV) refer to the beat-to-beat fluctuations of BP and heart rate, respectively, and baroreflex sensitivity (BRS) measures heart rate adaptations to rapid BP changes. The BPV, BRS and HRV reflect regulatory processes in the cardiovascular system and therefore allow the assessment of cardiac and vascular autonomic control.⁶ However, the underlying regulatory mechanisms are still

Received February 18, 2005. First decision August 8, 2005. Accepted August 18, 2005.

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This work was supported by the Deutsche Forschungsgemeinschaft (VO505/4-2, FA403-2) and the Federal Ministry of Education and Research (ProInno KF 0317302KLF3).

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poorly understood. Short-term BP regulation is mainly accomplished by neural sympathetic- and parasympathetic-mediated cardiac baroreflexes and peripheral vessel resistance, whereas long-term regulation is achieved by hormonal pathways such as the renin-angiotensin-system, body temperature, as well as other systems.⁷ The BPV, BRS, and HRV have proved to be independent predictors for sudden cardiac death after acute myocardial infarction,⁸ chronic heart failure,⁹ or dilated cardiomyopathy.^{10,11}

Currently there are first studies published that investigated autonomic cardiovascular control by means of BPV, BRS, and HRV in hypertensive pregnancy disorders, and especially in preeclampsia in order to derive risk markers.^{6,12} Normal pregnancy leads to hemodynamic changes, including a decreasing mean arterial pressure and peripheral vascular resistance, as well as increasing circulating volume, heart rate, and cardiac output. Studies investigating HRV and BRS under resting conditions in normotensive pregnant women during the second and third trimesters reported a reduced high-frequency (HF) component of HRV and a reduced BRS.^{13–16} In preeclampsia, however, the analyses of HRV and BPV revealed inconsistent results.⁶

To establish BPV, BRS, and HRV as predictors for preeclampsia and to reach a specificity superior to that achieved with Doppler sonography, it is necessary to investigate the impact of the abnormal uterine perfusion on cardiovascular control. To our knowledge, there is no study that particularly analyzes the influence of disturbed uterine perfusion. Because we hypothesize that abnormal uterine perfusion is associated with an altered maternal cardiovascular regulation, this study was designed to assess BPV, BRS, and HRV during the second half of gestation in pregnancies with normal or pathologic outcomes.

Methods

Subjects

In this longitudinal study, 32 healthy pregnant women with normal uterine perfusion (CON; age 28 years, range 24 to 30 years); 16 women with abnormal uterine perfusion and normal outcome (AP-NO; age 29 years, range 28 to 33 years), and 19 women with abnormal uterine perfusion and pathologic outcome (small-for-gestational-age infants without maternal hypertension, $N = 7$); pregnancy-induced hypertension, $N = 2$); and preeclampsia, $N = 10$); AP-PO; age 26 years, range 25 to 30 years) were recruited from the Department of Obstetrics and Gynecology, University of Leipzig, between June 2000 and December 2002. Initial BP was normal in all women. Maternal age, gravidity, and parity were comparable between all groups (Table 1). Furthermore, all pregnancies were singleton and without clinical signs of cervical incompetence. Hypertension was defined as one diastolic BP reading ≥ 110 mm Hg on any occasion or of one of ≥ 90 mm Hg on two consecutive diastolic BP readings ≥ 4 h apart. Significant

Table 1. Clinical parameters of control pregnancies (CON), pregnancies with abnormal perfusion, and normal outcome (AP-NO) and pregnancies with abnormal perfusion and pathologic outcome (AP-PO)

Parameter	CON (N = 32)	AP-NO (N = 16)	AP-PO (N = 19)	P*	P†	P‡
Maternal age (years)	28 (24–31)	29 (28–33)	26 (25–30)	.195	.106	.389
Initial systolic BP	111 (105–132)	133 (121–146)	130 (112–149)	.004	.401	.014
Initial diastolic BP	62 (55–67)	72 (64–83)	74 (61–87)	.003	.385	.015
Initial measurement (weeks)	20 (20–21)	20 (20–22)	21 (19–21)	.282	.529	.066
Parity	0 (0–1)	0 (0–1)	0 (0–1)	.741	.712	.389
Gravidity	2 (1–3)	1 (1–2)	1 (1–3)	.137	.477	.371
Mean uterine pulsatility index	0.78 (0.71–0.93)	1.48 (1.38–1.61)	1.76 (1.56–2.2)	<.001	.007	<.001
Rate of bilateral notch (%)	0	44	74	<.001	.024	<.001
Week of delivery	39 (39–40)	40 (39–41)	36 (34–38)	.175	<.001	<.001
Birth weight (g)	3490 (3110–3720)	3295 (3090–3581)	2020 (1615–2580)	.510	<.001	<.001
Rate of cesarean section (%)	22	25	79	.514	.004	.023
Rate of small-for-gestational-age infants %	0	0	58	.510	<.001	<.001
Hypertension disorder (%)	0	0	63	1.0	<.001	<.001

Data given as medians and interquartile ranges, Mann-Whitney U test or Fisher test for equality of proportions.

BP = blood pressure.

* CON v AP-NO; †AP-NO v AP-PO; ‡CON v AP-PO; significant values are set in boldface type.

proteinuria was defined ≥ 300 mg total protein in a 24-h urine collection or, if this was not available, positive proteinuria by dipstick on two consecutive occasions ≥ 4 h apart. Preeclampsia was defined as hypertension plus proteinuria. Newborns were defined as small-for-gestational-age infants if the birth weight was below the 10th percentile of an own-reference group.

The Doppler investigations of the uterine arteries were performed using a LOGIQ 9 ultrasound machine (GE, Solingen, Germany) with a 5-MHz convex transducer. The uterine perfusion was defined as pathologic if there was bilateral notching or if the mean pulsatility index of both uterine arteries was >1.45 .¹⁷ The Doppler measurement was performed in the 20th week, and in the cases of abnormal uterine perfusion, the persistence of this finding was validated in the 24th week.

The investigation conformed to the principles outlined in the Declaration of Helsinki. Local ethics committee approval and written informed consent of all subjects were been provided.

Data Acquisition and Preprocessing

After Doppler investigation in the 20th week of gestation, all women were monitored every 4th week until delivery. To analyze BPV, BRS, and HRV, non-invasive continuous BP recordings were taken simultaneously via a finger cuff (100-Hz, Portapres device, Model 2, BMI-TNO, Amsterdam, The Netherlands) and high-resolution ECG (1600 Hz).

All measurements were performed over 30 minutes under

standardized resting conditions between 8 AM and 12 PM¹⁸ as described before. From the Portapres recordings, time series of systolic as well as diastolic beat-to-beat pressure values were extracted to analyze BPV and BRS. From the ECG recordings, time series of beat-to-beat intervals (BBI) were extracted to analyze HRV. All time series were filtered to exclude ventricular premature beats and artifacts.

Analysis of HRV and BP

The parameters of time domain and frequency domain were calculated regarding to HRV task force standards as previously described.¹⁹ For spectral analysis, the time series were linearly interpolated by equidistant 500-msec samples. The power density spectra were estimated using fast-Fourier transform. To avoid leakage effects a Blackman-Harris window function was applied. Abbreviations and definitions of standard variability parameters are given in Table 2.

Baroreflex Sensitivity Analysis

The BRS was estimated using the sequence method.²⁰ Beat-to-beat series of systolic BP were scanned to identify a “sequence,” ie, a series of ≥ 3 heart beats in which a monotonic decrease of systolic pressure (>1 mm Hg) is followed by a monotonic decrease of BBI (>5 msec), ie, the time intervals between the instances of occurrence of consecutive systolic peaks. The slope of the regression line

Table 2. Abbreviations and definitions of standard heart rate (blood pressure) variability parameters according to the Heart Rate Variability (HRV) Task Force

	Unit	Description
HRV		Heart rate variability
BBI		Beat-to-beat interval
BRS	msec/mm Hg	Baroreflex sensitivity (please see its definition in the methods section)
Time domain		
meanNN (smeanNN, dmeanNN)	ms (mm Hg)	Mean beat-to-beat interval (systolic, diastolic blood pressure)
SDNN (bSDNN)	ms (mm Hg)	Standard deviation of all beat-to-beat interval/systolic blood pressure values
RMSSD (bRMSSD)	ms (mm Hg)	The square root of the mean of the sum of all squares of differences between adjacent beat-to-beat interval/systolic blood pressure values
Frequency domain		
VLF (bVLF)	s ² (mm Hg ²)	Power of beat-to-beat interval/systolic blood pressure time series in the very low frequency range (0.003–0.04 Hz)
BLF	mm Hg ²	Power of systolic blood pressure time series in the low frequency range (0.04–0.15 Hz)
LFn	n.u.	Power of beat-to-beat interval time series in the low frequency range (0.04–0.15 Hz) in normalized units; $100 \times \text{LF}/(\text{LF} + \text{HF})$ with HF as power of beat-to-beat interval time series in the high frequency range (0.15–0.4 Hz)

n.u. = no unit.

between BBI and systolic pressure values of each sequence gives a local estimate of the baroreflex sensitivity.

Statistical Analysis

To assess pregnancy-induced changes of autonomic control, we formed five groups regarding the monthly interval of monitoring: 1) 18 to 22 wG: 20th week of gestation; 2) 23 to 26wG: 24th week of gestation; 3) 27 to 30wG: 28th week of gestation; 4) 31 to 34wG: 32nd week of gestation; and 5) 35wG-end: 37th week of gestation.

The nonparametric Kruskal-Wallis-Test was applied to CON and AP-NO, as well as to AP-PO, to test whether the parameter changes significantly during the investigated intervals of gestation. The Friedman test for repeated measurements could not be applied because monthly recording was not always available. Furthermore, the nonparametric *U* test was used for group comparisons between CON, AP-NO, and AP-PO by means of their monthly medians. The significance level was set at $p < .05$.

Results

Patient Characteristics

Initial systolic and diastolic BP was slightly increased in pregnancies with abnormal perfusion (Table 1). Within the groups with abnormal perfusion, the mean pulsatility index of uterine arteries was significantly higher in women with AP-PO compared with those of women with AP-NO, whereas the rate of notches did not differ. Week of delivery and birth weight were significantly altered in AP-PO but not in AP-NO, compared with CON. Also the rate of cesarean section and rate of small-for-gestational-age infants were significantly increased only in AP-PO.

Variability of BP

In CON, the systolic BP did not significantly change during gestation (smeanNN, Fig. 1A), whereas the diastolic BP increased during the second half of pregnancy (dmeanNN, Fig. 1B). The spectral analysis of BPV revealed significant increases in the very-low-frequency component (bVLF) (Fig. 1E) and the low-frequency component (bLF) (Fig. 1F). On the contrary, the time domain parameters showed no significant alterations in CON (bSDNN and bRMSSD) (Figs. 1C, 1D).

Neither AP-NO nor AP-PO BPV significantly changed during gestation. However, the intergroup comparison among CON, AP-NO, and AP-PO showed a significant elevation in systolic BP in pregnancies with abnormal perfusion and an increased diastolic BP in women with a pathologic outcome. Overall, variability in BP (bSDNN) was increased in AP-PO as compared with CON, and short-term variability (bRMSSD) was increased in all pregnancies with abnormal perfusion.

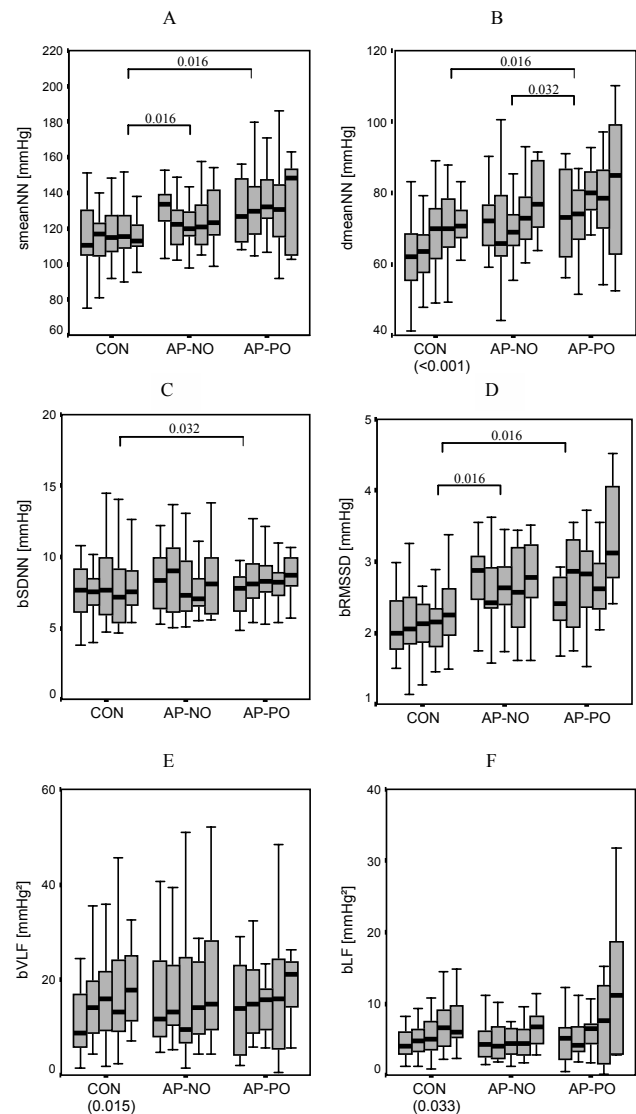


FIG. 1. Blood pressure parameters in normal pregnancies (CON) and pregnancies with abnormal uterine perfusion with normal (AP-NO) and pathologic outcome (AP-PO) during the second half of gestation according to the monthly interval of monitoring, represented as medians and quartiles. Significance within groups is marked at the group labels; significance between groups is marked with brackets.

Baroreflex Sensitivity

The BRS decreased continuously during the second half of gestation in CON (Fig. 2). In women with abnormal perfusion, BRS remained constant. Significant elevation of BRS however, was found in AP-PO as compared with CON and AP-NO.

HRV

In the HRV analysis (Fig. 3), an increase in heart rate (decreased meanNN) was found during the second half of pregnancy in CON (Fig. 3A). The time domain analysis of HRV parameters revealed a decreasing RMSSD (Fig. 3C) in CON. In the frequency domain, VLF (Fig. 3D) and LFN

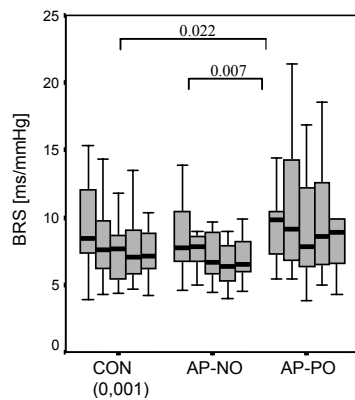


FIG. 2. Baroreflex sensitivity in normal pregnancies (CON) and pregnancies with abnormal uterine perfusion with normal (AP-NO) and pathologic outcome (AP-PO) during the second half of gestation according to the monthly interval of monitoring, represented as medians and quartiles. Significance within groups is marked at the group labels; significance between groups is marked with brackets.

(Fig. 3E) rose significantly in CON during pregnancy. On the contrary, no HRV parameter changed significantly in the course of gestation in AP-NO and AP-PO, respectively. No intergroup differences in HRV were observed between CON and AP-NO. The comparison of AP-PO with CON and AP-NO, however, revealed a significant increase in meanNN as well as RMSSD. In comparison to AP-NO, the AP-PO group showed a significantly increased SDNN (Fig. 3B).

Discussion

In previous studies, it was demonstrated that the parameter domains of BPV, BRS, and HRV reflect pregnancy-induced adaptations of autonomic cardiovascular control.⁶ Thus it was concluded that these methods could be a useful tool to detect pathophysiologic changes, particularly those in the hypertensive pregnancy disorder preeclampsia. However, the results of studies conducted by different authors have been inconsistent.⁶ Because pregnancies with hypertension or intrauterine growth restriction are mostly announced by abnormal uterine perfusion around the 20th week of gestation, we analyzed the influence of abnormal perfusion on BPV, BRS, and HRV during the second half of gestation, comparing normotensive pregnancies with normal uterine perfusion with pregnancies with abnormal perfusion and normal and pathologic outcomes.

The basal measurements of BP showed that normal pregnancies are characterized by unaltered systolic but increasing diastolic BP during the second half of pregnancy, which is a well-known finding in normal pregnancy.²¹ On the contrary, systolic and diastolic BPs were elevated in pregnancies with abnormal perfusion and might be a response of the poorly developed vascular system to optimize uterine perfusion and fetal oxygen supply. The even-higher elevated diastolic BP in pregnancies with pathologic outcome, es-

pecially during the last weeks of gestation, indicate a higher degree of disturbance in the vascular system and the consequent development of a hypertensive disorder or intrauterine growth restriction or both. The analysis of BPV in CON revealed increases in the vasomotor activity (bVLF and bLF) during the second half of pregnancy. The increased very-low-frequency oscillations (bVLF) might reflect the pregnancy-induced superimposed changes of various circulating vasoactive substances where the increased low frequency oscillations (bLF) are a consequence of an increased sympathetic activity and correspond to an increased muscle sympathetic nerve ac-

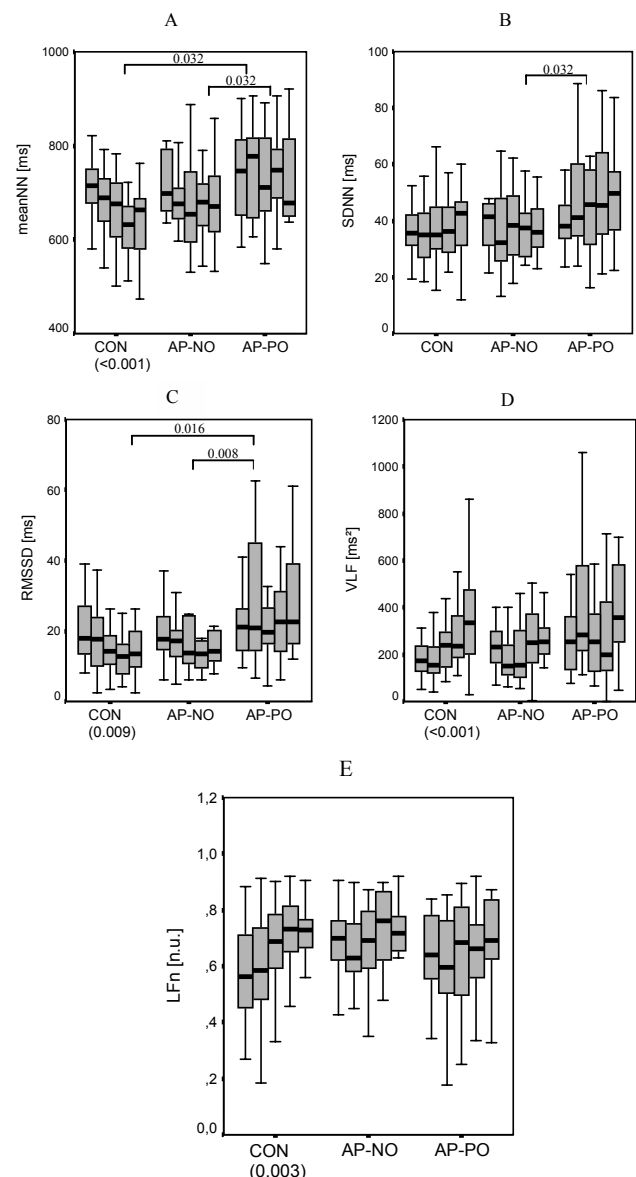


FIG. 3. Significantly altered heart rate variability parameters in normal pregnancies (CON) and pregnancies with abnormal uterine perfusion with normal (AP-NO) and pathologic outcome (AP-PO) during the second half of gestation according to the monthly interval of monitoring, represented as medians and quartiles. Significance within groups is marked at the group labels; significance between groups is marked with brackets.

tivity that was observed in normal pregnancies via microneurography during the third trimester.²² In pregnancies with abnormal perfusion, the adaptation of bVLF was not observed and might reflect the disturbed synthesis of vasoactive substances such as NO and prostacyclin.²³ Further on, no significant bLF adaptation was observed in pregnancies with abnormal perfusion but pregnancies with pathologic outcome showed in trend increasing low-frequency oscillations (bLF) suggesting an elevating sympathetic activity, although microneurography showed more increased sympathetic nerve activity in pregnancy-induced hypertension compared with normal pregnancies.²² The increased beat-to-beat fluctuations of systolic BP (bRMSSD) seem to be a direct cardiac response of the elevated systolic and diastolic pressure and the resulting hemodynamics (ie, an increased afterload).

In agreement with other authors, we found a decreasing BRS in the course of gestation of normal pregnancies.⁶ On the contrary, BRS did not significantly change in pregnancies with abnormal perfusion during the second half of gestation. Interestingly, BRS was even increased in AP-PO as compared with CON and AP-NO. This might be a direct consequence of the lower heart rate in AP-PO, allowing more vital response to rapid BP changes.

Analysis of HRV revealed an increase in mean heart rate and consequently a decreased HRV in CON during the second half of pregnancy, which agrees with earlier studies investigating heart rate in healthy pregnancies.^{14,24} The increase in heart rate results from an increased cardiac output as a consequence of the elevated blood volume. The decreased beat-to-beat HRV mediated by vagal efferents and illustrated by Root Mean Square of Successive Differences (RMSSD) indicates a reduced respiratory sinus arrhythmia in the second and third trimesters. The frequency domain analysis revealed an increased LF_n (caused by a relatively reduced HF component of HRV), which is commonly seen as a marker of sympatho-vagal balance and also suggests a reducing vagal activity during the second half of gestation. The HRV parameters, however, did not show any significant adaptation of heart rate control in pregnancies with abnormal perfusion during the second half of pregnancy. The intergroup comparison of HRV between CON, AP-NO, and AP-PO showed significant differences from the beginning of monitoring. A study investigating HRV in pregnancies with normal and preeclamptic outcome found first signs of an altered sympatho-vagal balance in women with preeclamptic outcome already in the 1st trimester.²⁵ Importantly, in pregnancies with pathologic outcome, the mean heart rate is lower and its variability (SDNN, RMSSD) is significantly higher than in pregnancies with normal outcome.

Furthermore, the VLF power of HRV increased continuously in CON but not in pregnancies with abnormal perfusion. Because the VLF band of HRV is assumed to reflect influences of thermoregulatory processes and the renin-angiotensin system,²⁶ this finding might be the result of reduced vascular responsiveness to angiotensin II in

normal pregnancy because increased vascular sensitivity to angiotensin results in decreased blood flow to all organs.²⁷ Although circulating levels of angiotensin II may be normal during preeclampsia, there are studies indicating enhanced vascular responsiveness to angiotensin II in vessels.²⁸ Increased vascular angiotensin II responsiveness during preeclampsia, however, does not prove angiotensin II as an important endogenous mediator of the vasoconstriction or hypertension in preeclampsia. Thus, our data may indicate that the renin-angiotensin-system does not play the major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure,²⁹ and therefore, the VLF is not altered in pregnancies with abnormal perfusion.

Summarizing all observed changes, it becomes evident that abnormal uterine perfusion is associated with altered maternal autonomic cardiovascular control. This is already evident in the first half of pregnancy, as these alterations were visible with the first monitoring at the 20th week of gestation. The predominant reason might be found in the disturbed placental development followed by a developing endothelial dysfunction³⁰ with a disturbed balance of vasoconstrictors and dilators that inhibits normal pregnancy-induced adaptations of vascular resistance. Otherwise, the changes of cardiovascular variability in pregnancies with abnormal uterine perfusion may be seen as an attempt to compensate the decreased placental and fetal supply. Normal fetal outcome in part of the pregnancies with perfusion disturbance demonstrated that this mechanism is successful in some cases. However, at this point we cannot explain why some pregnancies with pathologic uterine perfusion develop pregnancy complications whereas others do not.

In conclusion, BPV, BRS, and HRV, combined with Doppler examination of the uterine arteries, may be used to predict the outcome of abnormal pregnancy such as preeclampsia. Consequently, the strategy of care of such high-risk pregnancies might be further improved if analyses of heart rate and BP are combined with Doppler sonography. Further studies are needed to demonstrate whether this approach can be established as a diagnostic tool early in pregnancy.

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