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RESEARCH ARTICLE

Alison K. Shea
Markad V. Kamath
Alison Fleming
David L. Streiner
Keith Redmond
Meir Steiner

The effect of depression on heart rate variability during pregnancy

A naturalistic study

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A.K. Shea, MSc, PhD · A. Fleming, PhD
M. Steiner, MD, PhD, FRCPC
CIHR Program: Maternal Adversity, Vulnerability and Neurodevelopment
Hamiltion (ON), Canada

A.K. Shea, MSc, PhD
M. Steiner, MD, PhD, FRCPC (✉)
Women's Health Concerns Clinic
St. Joseph's Healthcare
50 Charlton Avenue East
L8N 4A6 Hamilton (ON), Canada
Tel.: +1-905/522-1155 ext -3605
Fax: +1-905/521-6098
E-Mail: mst@mcmaster.ca

A.K. Shea, MSc, PhD · D.L. Streiner, PhD
M. Steiner, MD, PhD, FRCPC
Institute of Medical Sciences
University of Toronto
Toronto (ON), Canada

M.V. Kamath, PhD · K. Redmond, B. Eng
Dept. of Medicine
McMaster University
Hamilton (ON), Canada

D.L. Streiner, PhD
Kunin-Lunenfeld Applied Research Unit
Baycrest Centre
Toronto (ON), Canada

A. Fleming, PhD
Dept. of Psychology
University of Toronto
Toronto (ON), Canada

D.L. Streiner, PhD
M. Steiner, MD, PhD, FRCPC
Dept. of Psychiatry
University of Toronto
Toronto (ON), Canada

D.L. Streiner, PhD
M. Steiner, MD, PhD, FRCPC
Dept. of Psychiatry and Behavioural Neurosciences
McMaster University
Hamilton (ON), Canada

M. Steiner, MD, PhD, FRCPC
Dept. of Obstetrics and Gynecology
McMaster University
Hamilton (ON), Canada

Abstract Depression during pregnancy has been associated with a number of adverse outcomes, but the underlying physiological mechanisms involved remain unclear. The purpose of this study was to examine the effects of maternal depression during pregnancy on the autonomic modulation of heart rate, in a naturalistic setting. Eighty-one pregnant women were studied between 25 and 31 weeks of gestation and were identified as either *Depressed* (n = 46), or healthy, *Control* (n = 35), based on depression scores and lifetime psychiatric history. Subjects wore a 24-h Holter recorder to measure time-domain and frequency-domain of heart rate variability (HRV). Pregnant women in the *Depressed Group* had significantly reduced time-domain measures: standard deviation of all 24-h NN intervals (SDNN) and the standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN) (P = 0.013, 0.016, respectively), as well as higher heart rates while asleep (P = 0.028), compared to *Controls*, after controlling for age, smoking, and antidepressant (AD) medication. The low frequency/high frequency (LF/HF) ratio during the sleeping hours was associated with higher depression scores (R = 0.24; P = 0.041). HRV measures improved in women taking AD medication. The autonomic nervous system may be affected in women experiencing depression during pregnancy, indicating a possible decreased parasympathetic (vagal) influence. Women taking AD medication showed some improvement in HRV measures. These data suggest that psychophysiological changes occur in women experiencing depression during pregnancy.

Key words pregnancy · heart rate variability · depression · anxiety · antidepressant

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Introduction

Although pregnancy is thought by many to be "protective" in terms of mental health and well-being, recent cohort studies have reported a similar incidence of depression and anxiety during gestation as in the postpartum period [3, 29]. Depression, anxiety, as well as stress during pregnancy have been associated with a number of adverse outcomes, including preeclampsia, premature delivery, fetal growth restriction, decreased mental and motor development and difficult infant temperament [26, 41, 54]. However, not all studies agree with these observations [4] and it is unclear why some infants born to women experiencing adversity remain resilient.

We suggest that physiological correlates may explain the shared negative sequelae of depression, stress, and anxiety during pregnancy. Both the sympathetic branch of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated during acute stress to promote adaptation, but also show dysregulation in depressed patients [19]. A common finding in depression is the loss of normal ANS control of heart rate and rhythm, as reflected in decreased heart rate variability (HRV) [1, 21]. The beat-to-beat HRV signal derived from an electrocardiogram (ECG) recording offers a unique, noninvasive measure of the effects of centrally mediated changes in autonomic modulation of cardiac function and is a reliable marker of ANS activity [31]. Decreased HRV may indicate a loss of vagal or parasympathetic modulation and a lack of the systems' ability to respond in a flexible manner, indicating vulnerability to the negative effects of stress [40].

In healthy pregnant women, HRV is reduced, while the mean 24-h heart rate (HR) is increased [45]. Flexible ANS function is essential to allow for changes in blood volume and circulation that take place during pregnancy. Poor adaptation of maternal hemodynamics may affect utero-placental circulation and subsequent fetal development. In particular, changes in umbilical blood flow velocity are purported as mainly determined by maternal hemodynamics, including the vascular pressure changes associated with maternal heart rate [41]. Women with abnormal uterine perfusion were found to have reduced HRV compared to healthy women and gave birth to infants of smaller birth weight [55]. A similar outcome was found in women experiencing stress and depressed mood during pregnancy [38]

The aim of this study was to examine the effects of maternal depression during pregnancy on ANS function. We recorded HR, which was then analyzed using time-domain and frequency-domain methodologies in order to derive parasympathetic modulation of HR. We hypothesized that women with prenatal depression would exhibit higher HR, decreased parasympathetic modulation, and a general pattern of increased sympathetic tone. Since depression is associated with sleep disturbances, it was hypothesized that these effects would be more pronounced during the night.

Materials and methods

This study was approved by the Research Ethics Board of St. Joseph's Healthcare and written informed consent was obtained for each participant. Pregnant women presenting to the Women's Health Concerns Clinic (WHCC) with depressed symptoms at 12–24 weeks of gestation (mean = 19.8 week) were recruited and offered a choice of treatments/interventions (*Depressed Group*). The study was naturalistic in design, and subjects were recruited via standard psychiatric clinical care visits. It was therefore not possible, nor ethical to follow depressed women prospectively though pregnancy without treatment intervention. Control subjects were recruited through flyers posted in the community and in our Ultrasound Department, Hamilton (*Control Group*). Inclusion criteria were: age of 18 years; pregnant (up to 24 weeks of gestation) and able to communicate in English. Further inclusion criteria for the *Depressed Group* were to score as "depressed," using one of the following cut-offs: Edinburgh postnatal depression scale (EPDS) score of ≥13 [11, 33] or the Montgomery-Asberg Depression Rating Scale score of ≥9 [36]. Assuming the comorbidity between depression and anxiety [16], prenatal anxiety was measured using the Spielberger state-trait anxiety inventory (STAI) [46].

Women with a current diagnosis or history of psychotic disorder were excluded, as well as those with serious medical conditions. Potential control subjects were excluded if they had a current or past diagnosis of psychiatric illness, as assessed by the Mini International Neuropsychiatric Interview (MINI) [43] and/or they had at least two stressful life events in the last 6 months (including relationship stress) as measured using the Interview for Stressful Life Events [39].

The participants wore a 24-h ECG Holter recorder (DelMar Avionics, Irvine, CA) during the early 3rd trimester (range: 25–31 weeks gestation, mean = 27.2 weeks), during the course of a normal day. Subjects were instructed to record the start and finish times of sleep, meals, work, resting time, physical activities, emotionally triggering events and other possibly relevant activities that may affect heart rate. For the current analyses, sleeping time was defined as the time 1 h after sleep started and 1 hour before awakening, as recorded in the activity diary [53]. Participants also repeated the EPDS and the STAI (State) to measure current mood state.

The 24-h Holter ECG recordings were analyzed by an experienced technologist blinded to group membership at the McMaster University Electrocardiography laboratory. The data was first annotated with Delmar Avionics scan software, and the beat-to-beat recognition software assigned a class (normal or ectopic) to each beat. All interbeat intervals were downloaded for offline computational analyses. The following time domain variables were obtained: the mean values for the standard deviation of all 24-h NN intervals (SDNN), the SD of the averages of NN intervals in all 5-min segments of the entire recording (SDANN), the % of NN intervals differing by more than 50 ms (pNN50) and the root mean square of the SD of successive NN intervals (rMSSD). The SDNN and the SDANN values are influenced by short-term (i.e.- respiration) and long-term (circadian) factors. The pNN50 and the rMSSD reflect vagal cardiac modulation under normal conditions [47].

The RR intervals from the 24-h recording were divided into one-hour segments. Each hourly RR interval data was divided into 128-s segments. A power spectrum of heart rate time series was derived from beat-to-beat changes in heart rate to identify the high frequency (HF: 0.15–0.4 Hz) power and low frequency (LF: 0.04–0.15 Hz) power bands. The HF power is related to respiratory sinus arrhythmia, reflective of cardiac vagal function, whereas the LF power is mediated by both the vagal and sympathetic systems [2]. Abnormal beats were interpolated with an interpolation algorithm. The software for the present study has been used in our laboratory previously. An eighth order auto-regressive model was used on the HRV signal and the power spectra of the model were annotated for each 128-s segment.

The hourly data were analyzed individually using Power Spectral Analyses, for a frequency range of 0.05–0.4 Hz. The power within two frequency bands were integrated and presented as: LF and HF. A visual inspection of the frequency bands was performed for each 1-h segment, and only hours with at least 12 power spectra of 128 s each (~30 min) were included. The spectral components were calculated as absolute units, and also as percentages (calculated by dividing LF and HF powers by their sum, and multiplying by 100). The main quantitative indices computed from the HRV signal were: HR, HF, and LF absolute area (ms^2); LF/HF area ratio.

Studies of 24-h HRV indicate a circadian influence on both the parasympathetic (HF) and sympathetic, as measured via pre-ejection period, control of the heart [10]. A shift to vagal dominance is seen during the night; daytime and sleep hours were consequently separated for analyses. The values derived from the power spectral analyses were averaged across daytime hours (09:00–21:00).

Statistics

The baseline characteristics were compared between groups using the independent *t* test (age, EPDS, STAI) and the chi-square test (partner status, parity). The frequency-domain values were transformed using Log10 to normalize the distribution before analyses. The mean 24-h time domain values (pNN50, SDNN, rMSSD, SDANN), as well as the frequency domain values (HR, log-transformed LF and HF, LF/HF ratio: 24-h, daytime only (09:00–21:00 h) and sleeping values (as per diary)) were compared using MANCOVA, using group (*Depressed* versus *Control*) as the between-subject factors. As age [8], body-mass index (BMI) [52], depression and anxiety [57] can influence HRV, Pearson correlations were used to examine possible effects on HRV values (variables: age, pre-pregnancy BMI, EPDS, STAI scores; 24-h: pNN50, SDNN, rMSSD, SDANN, HR, absolute LF and HF, LF/HF ratio, total power). Age was the only variable that was found to be significant, and was subsequently used as a covariate. Since both smoking and anti-depressant (AD) use [12, 17] can influence HRV parameters, these variables were used as covariates. The MANCOVA test was repeated after stratifying the *Depressed Group* according to current AD use. The Wilks' Lambda value is reported when a significant effect was found for the multivariate tests. The *F*-values and associated *P*-values are reported as appropriate. Unadjusted means and associated standard deviations (SD) are reported; raw frequency domain values are presented rather than the log-transformed values for comparison to other studies. Since 15 variables were tested in the MANCOVA for the frequency-domain indices, the Bonferroni test for multiple comparisons was used, and associated *P*-values were reported. Linear regression analyses were completed to examine the associations between the log-transformed LF/HF ratio values for the 24-h period, daytime and sleeping hours and current depression (EPDS) and anxiety (STAI) scores; the LF/HF ratio was selected to represent the sympatho-vagal balance, to limit the number of dependent variables. Tests for asphericity of data were performed and the Huynh-Feldt adjustment was used, as needed. Differences were considered significant at $P \leq 0.05$.

Results

Eighty-one women with singleton pregnancies completed the 24-h HRV recording: 46 who qualified for the *Depressed Group* and 35 in the *Control group*. Of the 46 women in the *Depressed Group*, 26 were treated using psychotherapy only, and 20 were treated using psychotherapy in combination with AD. Table 1 describes baseline demographics. A variety of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were used, the specific kind selected on a case-by-case basis by the attending psychiatrist. At the time of HRV monitoring, 2 subjects had been taking the ADs for 1.5 weeks; the remaining 18 had been taking the ADs for at least four weeks. There were no significant differences on EPDS or STAI scores between the *Depressed Group* taking ADs at time of ECG assessment compared to those who did not (Table 2).

24-h time domain analyses

The *Depressed Group* had lower values for all of the 24-h HRV measures, controlling for age, AD use and the number of cigarettes smoked per day (See Table 3,

Table 1 Baseline (14–24 weeks gestation) subject demographics (Mean (SD))

Group	Control ($N = 35$)	Depressed ($N = 46$)	*P*
Age (years)	31.6 (4.4)	29.3 (5.3)	0.04
% Married/common-law	100%	89.10%	0.07
% nulliparous	58.70%	48.60%	0.38
BMI (kg/m)	23.7 (4.3)	26.5 (6.2)	0.03
EPDS score	3.3 (2.2)	14.4 (5.2)	<0.0001
MADRS score	2.7 (1.4)	16.9 (5.7)	<0.0001
STAI (state) score	26.7 (6.5)	47.0 (14.2)	<0.0001

Table 2 Subject information at time of HRV analyses (mean (SD))

Group	Control ($N = 35$)	Depressed ($N = 26$)	Depressed + AD ($N = 20$)
Gestation (weeks)	27.5 (1.1)	27.4 (1.3)	26.3 (1.3)
EPDS score	3.2 (2.1)	11.0 (5.2)	13.1 (5.3)
STAI (state) score	27.5 (5.8)	42.8 (14.9)	50.8 (13.4)

Table 3 Unadjusted means (SD) for the 24-h HRV time domain measures in pregnant women

Group	Control ($N = 35$)	Depressed ($N = 46$)	*P*
pNN50 (%)	8.0 (9.6)	5.4 (5.4)	0.09
SDNN (ms)	112.4 (31.7)	97.9 (21.8)	0.01
SDANN (ms)	96.6 (30.0)	85.4 (23.6)	0.02
rMSSD (ms)	26.6 (13.0)	23.9 (9.0)	0.18

When the depressed group was stratified according to AD use, the differences on the SDNN and SDANN were only significant when comparing those not taking ADs and the controls

Fig. 1). Multivariate test indicated a group effect (Wilks' Lambda: 0.88; $F_{(4,73)} = 2.46$; $P = 0.05$). Univariate tests showed that two variables, SDNN and SDANN, were significantly lower in the *Depressed Group* ($F_{(1,76)}$ –values = 6.40, 6.04, respectively; *P*-values = 0.013, 0.016, respectively). When the *Depressed Group* was stratified according to AD use, the differences on the SDNN and SDANN were significant only when comparing the *Depressed Group* not taking AD versus controls ($F_{(2,76)} = 3.21$; $P = 0.040$; $F_{(2,76)} = 3.13$; $P = 0.049$, Fig. 2), respectively; *P*-values are adjusted for multiple comparisons, using the Bonferonni test), indicating improved HRV with AD use. Neither the EPDS, nor the STAI (state) were correlated with any of the 24-h time domain measures, controlling for age, smoking and AD use. Analyses were repeated using BMI as a covariate, and the results did not differ substantially.

Frequency domain analyses

The MANCOVA test was used to compare the frequency-domain variables (24-h; daytime hours

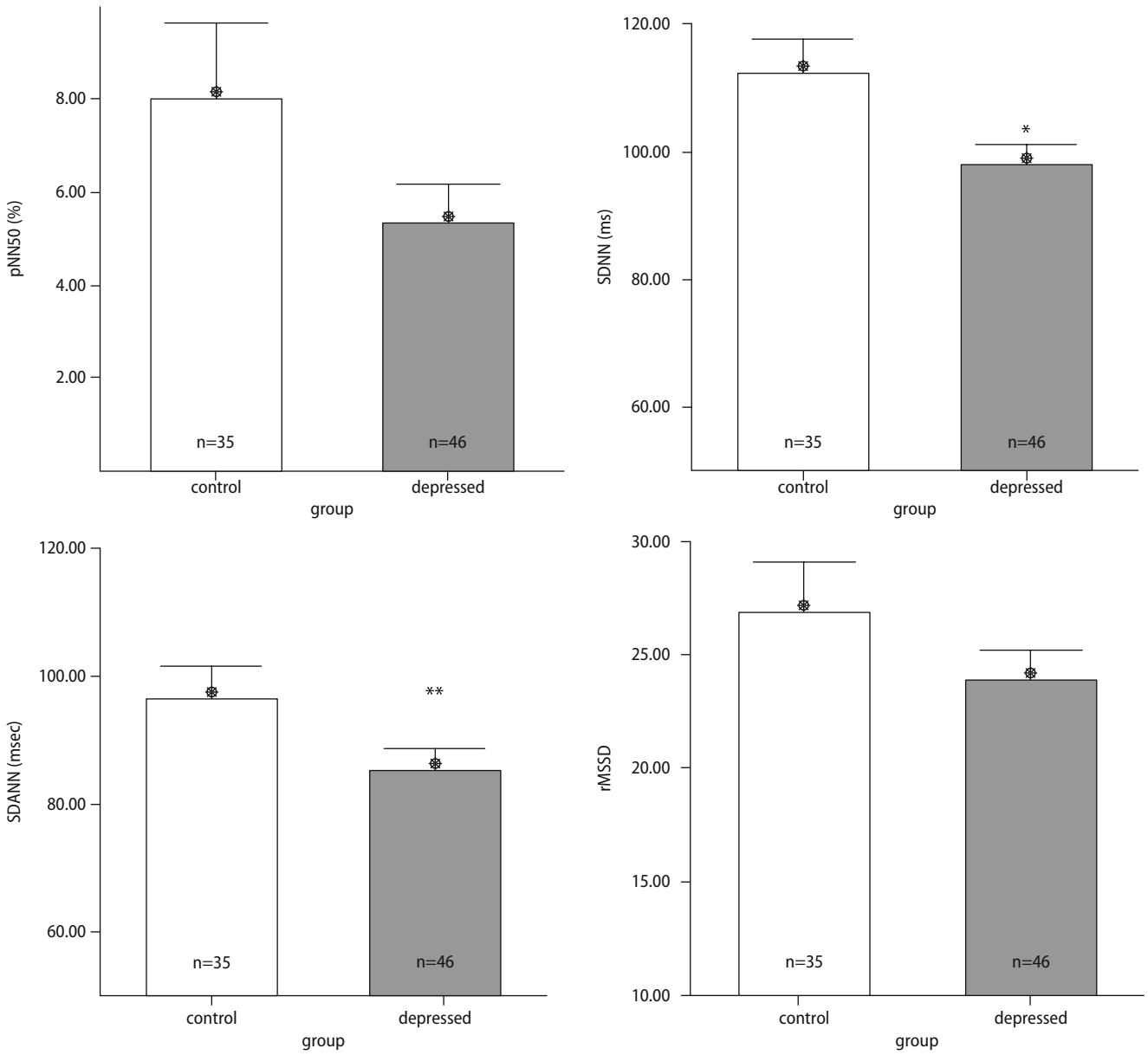

Fig. 1 Mean (±SE) time-domain HRV variables for healthy pregnant women (controls) and women who had experienced depression during pregnancy Groups were compared using MANCOVA, controlling for age, the number of cigarettes smoked per day and current anti-depressant use. (*$P = 0.01$ **$P = 0.02$)

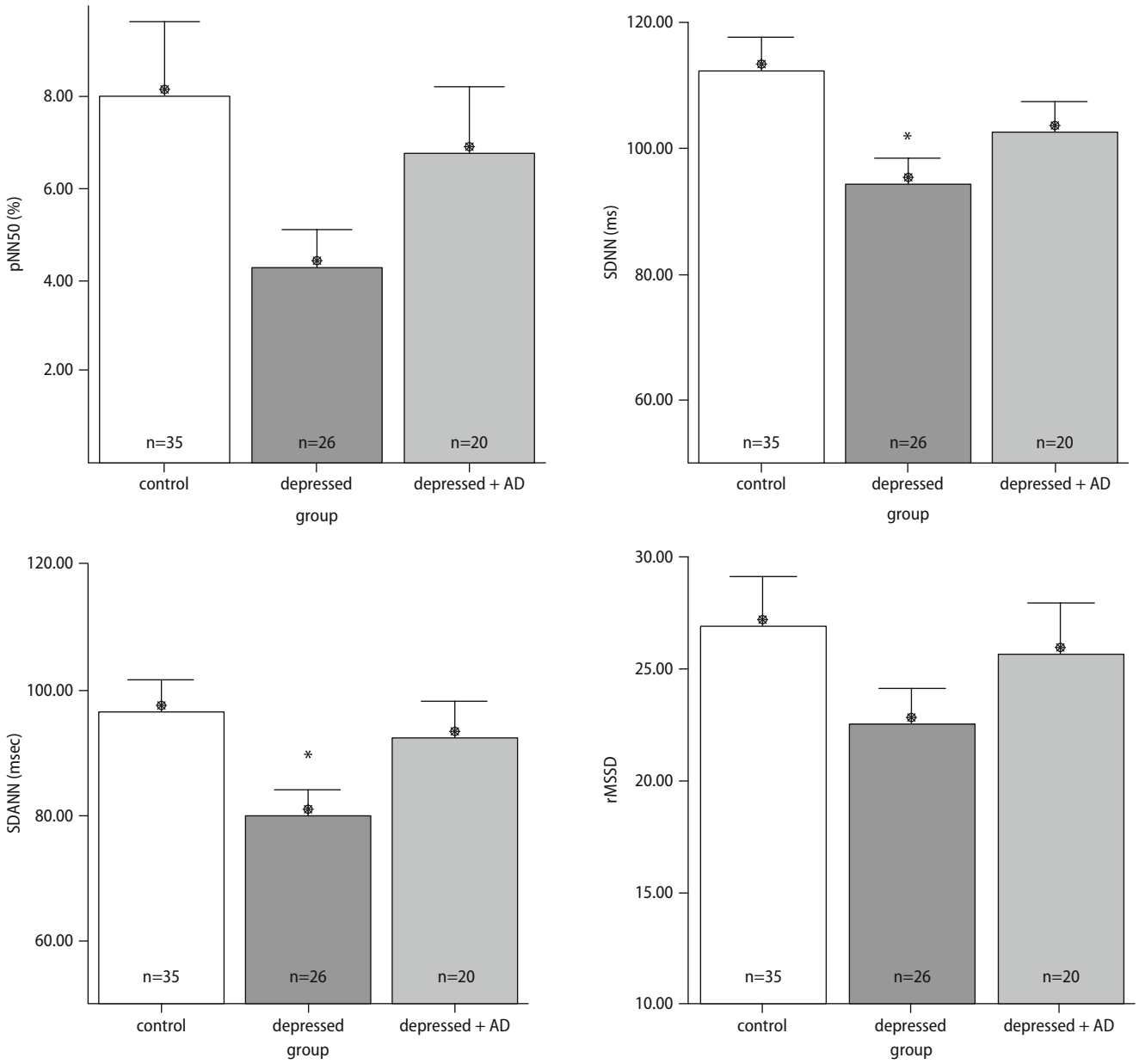

Fig. 2 Mean (±SE) HRV time domain variables in pregnant women by group, stratified according to current anti-depressant (AD) use. *$P < 0.05$ versus controls

and sleeping hours) using group (*Depressed* versus *Control*) as the between-subject factors and the same covariates. One subject had missing RR interval data; the daytime and mean 24-h frequency domain analyses were completed for $n = 80$; two additional subjects had missing data for sleeping hours and analyses were completed for $n = 78$. Multi-variate tests indicated no overall significant effect of group, age, number of cigarettes smoked, or AD medication.

There were no significant differences between the groups on the 24-h, daytime (09:00–21:00 h) or sleeping time (as per diary) frequency domain measures. Unadjusted means are presented in Table 4. However, univariate tests showed that HR, in particular, was significantly higher during the sleeping hours in the *Depressed Group* versus controls ($F_{(1,73)} = 5.05$; $P = 0.028$). When the *Depressed Group* was stratified according to AD use, the difference (trend) was observed only when comparing the *Depressed* subjects not taking AD versus controls ($F_{(2,73)} = 2.53$; $P = 0.093$; Fig. 2), indicating a possible improvement in HR with AD use. Linear regression analyses indicated that the sleeping LF/HF ratio was positively associated with the EDPS scores, controlling for age, AD use and

Table 4 Unadjusted means (SD) for the HRV frequency domain values, by group

Group	Control (N = 35)	Depressed (N = 45)	P
Heart rate (bpm)			
24-h	85.6 (9.0)	88.6 (7.2)	0.16
Daytime	94.4 (9.8)	97.2 (9.9)	0.57
Sleeping hours	75.5 (9.2)	79.8 (6.6)	0.03
Absolute HF area			
24-h	4001.8 (623.6)	3937.9 (589.9)	0.3
Daytime	3670.4 (611.1)	3678.2 (526.6)	0.24
Sleeping hours	4533.5 (822.5)	4404.7 (863.2)	0.34
Absolute LF area			
24-h	6184.17 (383.3)	6228.9 (455.4)	0.67
Daytime	6467.3 (276.0)	6426.0 (275.8)	0.76
Sleeping hours	5709.8 (661.6)	5856.6 (834.8)	0.35
LF: HF ratio			
24-h	1.8 (0.4)	1.8 (0.4)	0.32
Daytime	2.0 (0.4)	2.0 (0.3)	0.84
Sleeping hours	1.5 (0.4)	1.6 (0.5)	0.2

Groups were compared using MANCOVA, controlling for age and current antidepressant use. The *P*-values are adjusted for multiple comparisons using the Bonferroni test

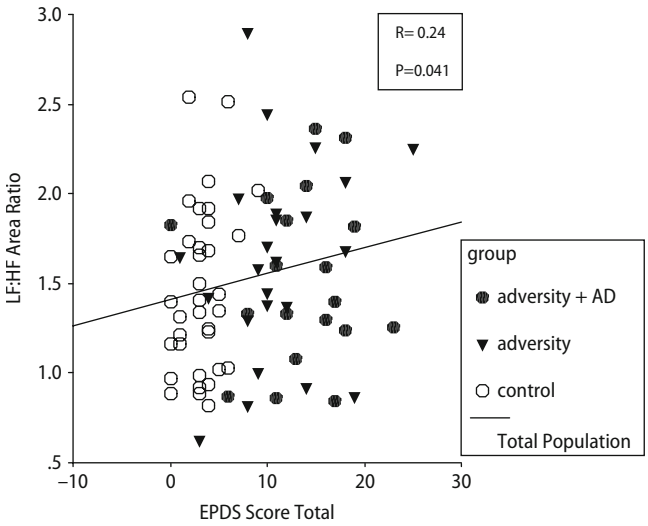

Fig. 3 The relationship between the LF/HF area ratio during the sleeping hours and scores on the Edinburgh postnatal depression scale (EPDS) at time of assessment in pregnant women

the number of cigarettes smoked per day (R = 0.24; β = 0.28; t = 2.08; P = 0.041, Fig. 3), but not with the anxiety (STAI) score. The 24-h and daytime LF/HF ratio were not significantly influenced by the EPDS or STAI scores. The group comparison analyses were repeated after excluding those taking SNRI (n = 5), and the results did not differ substantially.

Discussion

To our knowledge, this is the first attempt to measure heart rate variability in pregnant women experiencing depression. Our data suggest that maternal depression during pregnancy is associated with decreased HRV, particularly in the time domain measures, SDNN and SDANN. Depressed women taking AD medication had SDNN and SDANN values that were much closer to those observed in women who were healthy controls, indicating a positive effect of the treatment. However, it should be noted that the investigation of AD effects was a secondary analyses, which presents somewhat of a challenge for the interpretation of these effects in this naturalistic study.

We expected that we would see group differences in HRV during the sleeping hours, but this was limited to HR. Frequency domain indices did not differentiate the groups, which may be due to the known variability of these measures, and has been similarly reported elsewhere [7]. However, the LF/HF ratio (measure of sympatho-vagal balance) while the women were asleep, was influenced by the severity of the depression. Further investigation is required with respect to the frequency domain indices in relation to maternal depression during pregnancy.

Significant changes in the autonomic nervous system occur during pregnancy to accommodate the circulatory homeostatic requirements. Decreased HRV, particularly SDNN, has been reported for healthy pregnant women compared to non-pregnant controls at rest and during exercise [6, 48]. The SDNN reflects the balance between the sympathetic and parasympathetic input on the cardiac pacemaker; a reduced SDNN suggests a diminished parasympathetic (vagal) influence. Stein et al. [48] noted considerable variability in HRV during the course of a normal pregnancy, but a greatly diminished HRV may indicate ANS dysfunction, which may have consequences for healthy fetal development.

A decrease in HRV may be involved in the hemodynamic accommodation during normal pregnancy, but additional reductions have been reported for women with complications, such as preeclampsia (PE) and pregnancy-induced hypertension (PIH) [35, 56]. Pregnant women identified as high risk showed increased LF and LF/HF ratio during the 1st trimester, indicating changes early in gestation [5]. Our finding of an increased LF/HF ratio during the sleeping hours in women with higher depression scores may indicate a similar physiology. There is a lack of consensus on the role of HRV in PE but the sympathetic nervous system has been implicated in associated negative outcomes, such as reduced birth weight [37]. Reduced birth weight is also associated with maternal stress and depression [38, 41], which may present an important parallel to our findings of decreased SDNN/SDANN, as well as the improvement in values seen with AD use.

Increased sympathetic tone may effect the in utero environment

An imbalance of autonomic nervous system branches, in favor of sympathetic dominance due to maternal depression may affect the fetus. High maternal depression and anxiety during pregnancy have been found to increase fetal activity [14, 18]. A higher pulsatility index (PI), which rises with increasing vascular resistance, was found in the umbilical artery of fetuses of mothers with high trait anxiety scores [44]. Furthermore, high trait anxiety was associated with an increased mean artery resistance index compared to those with low trait anxiety [50], and it was suggested that such changes may explain the finding of low birth weight in infants born to mothers experiencing depression, stress, and anxiety. Similar studies have not been completed to our knowledge in women experiencing prenatal depression alone, but the results presented here may provide some clues to the underlying pathophysiology.

Changes in the maternal cardiovascular system during pregnancy can affect fetal heart rate [15, 30]. By using a fetal heart rate monitor over a 24-h period, Lunshof et al. [30] found that 73% of 15 fetuses had a diurnal heart rate rhythm, which was very similar to that of their mother. In a larger study, DiPietro et al. [15] reported an association between maternal and fetal HR and higher fetal HR was associated with lower HRV at 1 year of age. If the increased HR and decreased HRV in the Depressed subjects during pregnancy translates to similar changes in the fetus, the development of the fetal ANS may be compromised. Long-term follow-up and HRV measurement of infants born to these women is warranted.

The effect of depression on HRV parameters

Studies examining the effects of depression frequently report decreased HRV, in both the time and frequency domain parameters. Recently, it was reported that depressed patients exhibited reduced parasympathetic-related activity (high HR and reduced HF), as well as a diminished baroreceptor sensitivity (BRS) [13]. The EPDS score was positively associated with the LF/HF ratio during the sleeping hours in the current study, indicating decreased parasympathetic drive with higher depression scores.

The majority of HRV investigations with respect to mood are completed in patients with cardiovascular disease (CVD) wherein the pathophysiology differs significantly compared to pregnancy, making comparison challenging. The changes in hormone levels during pregnancy present an additional important variable. Of particular note however, women suffering from premenstrual dysphoric disorder (PMDD) showed reduced SDNN and HF compared to control women during the follicular phase of the menstrual cycle, when estrogen levels are high [27]. Increased estrogen levels, seen in both the follicular phase and pregnancy, may affect both the ANS balance and consequently, mood in vulnerable women. High prenatal estrogen levels may modulate ANS function, which may influence mood during pregnancy for some women. In attempt to understand the pathophysiological changes associated with mood dysregulation we must look to other available evidence from a neurochemical perspective. Higher levels of urinary and plasma SNS catecholamines, NE and Epi, have been reported in subjects experiencing chronic depression suggesting increased sympathetic drive [22, 23, 28, 42, 49], as well as women suffering from PE [25, 32]. If there is a sympathetic overdrive in our Depressed Group, it may be possible to normalize or improve the sympatho-vagal balance with effective treatment strategies.

Can AD treatment during pregnancy improve HRV?

When the Depressed Group was stratified according to current AD medication use, we saw that the differences in the sleeping HR and the time domain parameters (SDNN, SDANN) were significant only when comparing those not taking AD versus controls, indicating a possible improved sympatho-vagal balance with AD medication. A 6-month course of the SSRI, sertraline, in depressed patients led to a linear rate of increase in the SDNN together with a significant decrease in depression scores [34]. Also, a recent well-designed RCT showed that 16 weeks of sertraline treatment improved HRV measures [20]. A positive effect of the SSRI, paroxetine, on the LF/HF ratio and on baroreceptor responsiveness was found in patients with panic disorder [51]. It is possible that the AD medication in the Depressed subjects may be improving baroreceptor and vagal influence. This is highly significant because higher baroreceptor sensitivity during pregnancy indicates improved hemodynamic stability, which may assist with healthy placental perfusion [24]. Again, it must be mentioned that the examination of AD effects was a secondary analyses which limits the interpretation of these results. Nevertheless, the findings present an important observation that warrants further investigation.

Although we did not see a statistically significant effect of the AD medication on frequency-domain parameters, it is likely that our sample size may not have provided us with adequate power to detect these differences with only 20 women in this category. The

heterogeneity of medication used here, makes it difficult to generalize the results, or to indicate which type is beneficial for ANS function during pregnancy. As mentioned, the analyses were repeated after excluding the 5 women taking the SNRI type of AD medication, and the significant drug effect (i.e. now only SSRI AD medication) remained. Yet, it is an important possibility that depressed women may take these medications during pregnancy and all available data regarding the potential physiological effects during pregnancy are needed. If in fact AD medication improves HRV parameters, it will be interesting to see how the birth outcomes (particularly growth parameters) are influenced when this cohort is followed longitudinally. However, the decision for pregnant women to take AD medication needs to be assessed on an individual basis. There may be other ways to improve vagal modulation when AD medication is not appropriate. For example, one study found that cognitive behavioural therapy led to reduced HR and increased HRV among severely depressed patients with heart disease [9]. If the negative emotional stimuli or affect can be resolved, it may be possible to increase parasympathetic influence among women experiencing depression.

In conclusion, this study shows that women experiencing depression during pregnancy show significant decreases in HRV (SDNN and SDANN), indicative of decreased vagal tone during the early third trimester of pregnancy. Increased depression scores were associated with decreased vagal modulation and an improvement in HRV was demonstrated with AD treatment. Although we were limited in that we did not have a comparison group of depressed women receiving no treatment/intervention therapy, the study was naturalistic in design, and it would not be possible or ethical to follow pregnant women without offering standard clinical care. Long-term follow-up of this cohort will help to clarify whether these findings correlate with any of the birth outcomes, as well as the infant HRV.

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References

1. Agelink MW, Boz C, Ullrich H, Andrich J (2002) Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. Psychiatry Res 113:139–149
2. Akselrod S, Barak Y, Ben-Dov Y, Keselbrener L, Baharav A (2001) Estimation of autonomic response based on individually determined time axis. Auton Neurosci 90:13–23
3. Andersson L, Sundstrom-Poromaa I, Wulff M, Astrom M, Bixo M (2006) Depression and anxiety during pregnancy and 6 months postpartum: a follow-up study. Acta Obstet Gynecol Scand 85:937–944
4. Andersson L, Sundstrom-Poromaa I, Wulff M, Astrom M, Bixo M (2004) Neonatal outcome following maternal antenatal depression and anxiety: a population-based study. Am J Epidemiol 159:872–881
5. Antonazzo P, Cetin I, Tarricone D, Lombardi F, Pardi G (2004) Cardiac autonomic modulation in normal, high-risk, and in vitro fertilization pregnancies during the first trimester. Am J Obstet Gynecol 190:199–205
6. Avery ND, Wolfe LA, Amara CE, Davies GA, McGrath MJ (2001) Effects of human pregnancy on cardiac autonomic function above and below the ventilatory threshold. J Appl Physiol 90:321–328
7. Bar KJ, Greiner W, Jochum T, Friedrich M, Wagner G, Sauer H (2004) The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. J Affect Disord 82:245–252
8. Bonnemeier H, Richardt G, Potratz J, Wiegand UK, Brandes A, Kluge N, Katus HA (2003) Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. J Cardiovasc Electrophysiol 14:791–799
9. Carney RM, Freedland KE, Stein PK, Skala JA, Hoffman P, Jaffe AS (2000) Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosom Med 62:639–647
10. Carrington M, Walsh M, Stambas T, Kleiman J, Trinder J (2003) The influence of sleep onset on the diurnal variation in cardiac activity and cardiac control. J Sleep Res 12:213–221
11. Cox J, Holden JM, Sagovsky R (1987) Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale 150:782–786
12. Davidson J, Watkins L, Owens M, Krulewicz S, Connor K, Carpenter D, Krishnan R, Nemeroff C (2005) Effects of paroxetine and venlafaxine XR on heart rate variability in depression. J Clin Psychopharmacol 25:480–484
13. Davydov DM, Shapiro D, Cook IA, Goldstein I (2006) Baroreflex mechanisms in major depression. Prog Neuropsychopharmacol Biol Psychiatry 31:164–177
14. Dieter JN, Field T, Hernandez-Reif M, Jones NA, Lecanuet JP, Salman FA, Redzepi M (2001) Maternal depression and increased fetal activity. J Obstet Gynaecol 21:468–473
15. DiPietro JA, Costigan KA, Pressman EK, Doussard-Roosevelt JA (2000) Antenatal origins of individual differences in heart rate. Dev Psychobiol 37:221–228

16. Faisal-Cury A, Rossi Menezes P (2007) Prevalence of anxiety and depression during pregnancy in a private setting sample. Arch Womens Ment Health 10:25–32
17. Felber Dietrich D, Schwartz J, Schindler C, Gaspoz JM, Barthelemy JC, Tschopp JM, Roche F, von Eckardstein A, Brandli O, Leuenberger P, Gold DR, Ackermann-Liebrich U (2007) Effects of passive smoking on heart rate variability, heart rate and blood pressure: an observational study. Int J Epidemiol 36:834–840
18. Field T, Diego M, Hernandez-Reif M, Schanberg S, Kuhn C, Yando R, Bendell D (2003) Pregnancy anxiety and comorbid depression and anger: effects on the fetus and neonate. Depress Anxiety 17:140–151
19. Gillespie CF, Nemeroff CB (2005) Hypercortisolemia and depression. Psychosom Med 67(Suppl 1):S26–S28
20. Glassman AH, Bigger JT, Gaffney M, Van Zyl LT (2007) Heart rate variability in acute coronary syndrome patients with major depression: influence of sertraline and mood improvement. Arch Gen Psychiatry 64:1025–1031
21. Hughes JW, Stoney CM (2000) Depressed mood is related to high-frequency heart rate variability during stressors. Psychosom Med 62:796–803
22. Hughes JW, Watkins L, Blumenthal JA, Kuhn C, Sherwood A (2004) Depression and anxiety symptoms are related to increased 24-h urinary norepinephrine excretion among healthy middle-aged women. J Psychosom Res 57:353–358
23. James GD, Berge-Landry Hv H, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH (2004) Urinary catecholamine levels in daily life are elevated in women at familial risk of breast cancer. Psychoneuroendocrinology 29:831–838
24. Jayawardana MA (2001) Baroreceptor sensitivity and haemodynamics in normal pregnancy. J Obstet Gynaecol 21:559–562
25. Kaaja RJ, Moore MP, Yandle TG, Ylikorkala O, Frampton CM, Nicholls MG (1999) Blood pressure and vasoactive hormones in mild preeclampsia and normal pregnancy. Hypertens Pregnancy 18:173–187
26. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O (2000) Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 95:487–490
27. Landen M, Wennerblom B, Tygesen H, Modigh K, Sorvik K, Ysander C, Ekman A, Nissbrandt H, Olsson M, Eriksson E (2004) Heart rate variability in premenstrual dysphoric disorder. Psychoneuroendocrinology 29:733–740
28. Lechin F, van der Dijs B, Orozco B, Lechin ME, Baez S, Lechin AE, Rada I, Acosta E, Arocha L, Jimenez V, et al (1995) Plasma neurotransmitters, blood pressure, and heart rate during supine-resting, orthostasis, and moderate exercise conditions in major depressed patients. Biol Psychiatry 38:166–173
29. Levine RE, Oandasan AP, Primeau LA, Berenson AB (2003) Anxiety disorders during pregnancy and postpartum. Am J Perinatol 20:239–248
30. Lunshof S, Boer K, Wolf H, van Hoffen G, Bayram N, Mirmiran M (1998) Fetal and maternal diurnal rhythms during the third trimester of normal pregnancy: outcomes of computerized analysis of continuous twenty-four-hour fetal heart rate recordings. Am J Obstet Gynecol 178:247–254
31. Malik M (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the European Society of Cardiology and the North American Society of pacing and electrophysiology. Eur Heart J pp 354–381
32. Manyonda IT, Slater DM, Fenske C, Hole D, Choy MY, Wilson C (1998) A role for noradrenaline in pre-eclampsia: towards a unifying hypothesis for the pathophysiology. Br J Obstet Gynaecol 105:641–648
33. Matthey S, Henshaw C, Elliott S, Barnett B (2006) Variability in use of cut-off scores and formats on the Edinburgh postnatal depression scale: implications for clinical and research practice. Arch Womens Ment Health 9:309–315
34. McFarlane A, Kamath MV, Fallen EL, Malcolm V, Cherian F, GN (2001) Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. Am Heart J 142:617–623
35. Metsaars WP, Ganzevoort W, Karemaker JM, Rang S, Wolf H (2006) Increased sympathetic activity present in early hypertensive pregnancy is not lowered by plasma volume expansion. Hypertens Pregnancy 25:143–157
36. Mittmann N, Mitter S, Borden EK, Herrmann N, Naranjo CA, Shear NH (1997) Montgomery-Asberg severity gradations. Am J Psychiatry 154:1320–1321
37. Ophir E, Dourleshter G, Hirsh Y, Fait V, German L, Bornstein J (2006) Newborns of pre-eclamptic women: a biochemical difference present in utero. Acta Obstet Gynecol Scand 85:1172–1178
38. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Heinen AG, van Geijn HP (1999) Psychosocial predictors of low birthweight: a prospective study. Br J Obstet Gynaecol 106:834–841
39. Paykel ES (1997) The interview for recent life events. Psychol Med 27:301–310
40. Porges SW (1995) Cardiac vagal tone: a physiological index of stress. Neurosci Biobehav Rev 19:225–233
41. Rondo PH, Ferreira RF, Nogueira F, Ribeiro MC, Lobert H, Artes R (2003) Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. Eur J Clin Nutr 57:266–272
42. Sevy S, Papadimitriou GN, Surmont DW, Goldman S, Mendlewicz J (1989) Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. Biol Psychiatry 25:141–152
43. Sheehan D, Lecrubier Y, Sheehan HK (1997) The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 12:232–241
44. Sjostrom K, Valentin L, Thelin T, Marsal K (1997) Maternal anxiety in late pregnancy and fetal hemodynamics. Eur J Obstet Gynecol Reprod Biol 74:149–155
45. Speranza G., Verlato G, Albiero A (1998) Autonomic changes during pregnancy: assessment by spectral heart rate variability analysis. J Electrocardiol 31:101–109
46. Spielberger CD (1996) State-trait anger expression inventory: professional manual. Psychological Assessment Resources, Odessa
47. Stein PK, Bosner MS, Kleiger RE, Conger BM (1994) Heart rate variability: a measure of cardiac autonomic tone. Am Heart J 127:1376–1381
48. Stein PK, Hagley MT, Cole PL, Domitrovich PP, Kleiger RE, Rottman JN (1999) Changes in 24-h heart rate variability during normal pregnancy. Am J Obstet Gynecol 180:978–985
49. Takase B, Akima T, Satomura K, Ohsuzu F, Mastui T, Ishihara M, Kurita A (2004) Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels. Biomed Pharmacother 58(Suppl 1):S35–S39
50. Teixeira JM, Fisk NM, Glover V (1999) Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. BMJ 318:153–157

51. Tucker P, Adamson P, Miranda R Jr, Scarborough A, Williams D, Groff J, McLean H (1997) Paroxetine increases heart rate variability in panic disorder. J Clin Psychopharmacol 17:370–376
52. Vallejo M, Marquez MF, Borja-Aburto VH, Cardenas M, Hermosillo AG (2005) Age, body mass index, and menstrual cycle influence young women's heart rate variability—a multivariable analysis. Clin Auton Res 15:292–298
53. van Amelsvoort LG, Schouten EG, Maan AC, Swenne CA, Kok FJ (2000) Occupational determinants of heart rate variability. Int Arch Occup Environ Health 73:255–262
54. Wadhwa PD (2005) Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology 30:724–743
55. Walther T, Wessel N, Malberg H, Voss A, Stephan H, Faber R (2006) A combined technique for predicting pre-eclampsia: concurrent measurement of uterine perfusion and analysis of heart rate and blood pressure variability. J Hypertens 24:747–750
56. Yang CC, Chao TC, Kuo TB, Yin CS, Chen HI (2000) Preeclamptic pregnancy is associated with increased sympathetic and decreased parasympathetic control of HR. Am J Physiol Heart Circ Physiol 278:H1269–H1273
57. Yeragani VK, Rao KA, Smitha MR, Pohl RB, Balon R, Srinivasan K (2002) Diminished chaos of heart rate time series in patients with major depression. Biol Psychiatry 51:733–744