Eur J Appl Physiol (2002) 87: 309–314
DOI 10.1007/s00421-002-0634-0

ORIGINAL ARTICLE

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Changes of respiratory sinus arrhythmia during the menstrual cycle depend on average heart rate

Accepted: 27 March 2002 / Published online: 3 July 2002

Abstract To evaluate the complex time course of changes in respiratory sinus arrhythmia (RSA) during the menstrual cycle, daily beat-to-beat morning recordings of heart rate (HR) were carried out in 26 healthy female subjects (age 20–29 years) during two menstrual cycles. For determination of fast, vagally mediated variations of HR we used a robust time-domain measure of RSA (logRSA). We found pronounced changes in HR during the menstrual cycle with a minimum in the early follicular phase and a maximum in the late luteal phase. There were large differences between individuals in the fluctuations of logRSA during the menstrual cycle that were related to average HR: subjects with a low HR exhibited higher values of logRSA in the luteal compared to the follicular phase, whereas the trend was reversed in subjects with a high HR. The difference of extreme points of logRSA fluctuations (early follicular and mid luteal phase) was correlated to average HR ($r = -0.64$, $P < 0.001$). We conclude that different patterns of RSA fluctuations occur depending on the level of average HR.

Keywords Cardiac vagal control · Respiratory sinus arrhythmia · Autonomic nervous system · Female

Introduction

The menstrual cycle affects half of the world's population during several decades of their lives and is associated with pronounced physiological changes. Pregnancy can be seen as a prolongation of the luteal phase of the menstrual cycle. Diseases like emesis gravidarum and pre-eclampsia, which occur during pregnancy, are very likely associated with or even evoked by autonomic dysfunction. Despite this importance, physiological knowledge about cardiac autonomic control during the normal menstrual cycle is scarce. In earlier studies, several physiological parameters connected to autonomic activity like heart rate (HR, Döring and Feustel 1953; Hildebrandt and Witzenrath 1969; Kaplan et al. 1990; Kirsch and Geer 1988; Little and Zahn 1974; Manhem and Jern 1994) or galvanic skin response (Kirsch and Geer 1988; Little and Zahn 1974) were studied during the menstrual cycle. In recent years, highly sensitive approaches such as measurement of HR variability (HRV) have become available, which facilitate non-invasive investigations of cardiac autonomic control (Appel et al. 1989; Bigger et al. 1992; Lehofer et al. 1997; Moser et al. 1994, 1995; Porges 1986). For a detailed physiological background of HRV we refer to recent review articles (Berntson et al. 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). In brief, the high-frequency (HF) component of HRV is closely connected to respiratory sinus arrhythmia (RSA). Its frequency range corresponds to that of respiration. These relatively rapid fluctuations of R–R intervals (the time period between two heart beats) are thought to be mediated by parasympathetic cardiac nerves, and hence to represent an index of vagal control of the heart as seen from receptor blockade, vagotomy or tilt-table experiments (Berntson et al. 1997; Eckberg 1983; Pagani et al. 1986; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). More controversial is the interpretation of the low-frequency (LF) component of HRV, which is considered to be a marker of sympathetic outflow or as a parameter that includes influences from both autonomic branches (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology

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1996). HR and HRV are influenced by both parts of the autonomic nervous system in different ways, either directly or via humoral pathways, the net effect determining sinus node frequency at a particular time (Lehofer et al. 1997; Moser et al. 1998). In the present study, logRSA, a time-domain measure representing the HF component of HRV, was used as an index of cardiac vagal tone (Lehofer et al. 1997; Moser et al. 1994, 1998; Strauss-Blasche et al. 2000).

There is increasing evidence that cardiac autonomic control, and hence HRV, is influenced by changing levels of the female sex hormones, as occurs during the menstrual cycle (Guasti et al. 1999; Saeki et al. 1997; Sato et al. 1995), pregnancy (Kuo et al. 2000; Lucini et al. 1999; Stein et al. 1999) or menopause (Brockbank et al. 2000). Previous investigations have reported increased values for the HF component of HRV in the follicular phase compared to the luteal phase (Guasti et al. 1999; Sato et al. 1995) or the menstrual phase (Saeki et al. 1997). However, the data were collected only once a week (Saeki et al. 1997) or at two time points (Guasti et al. 1999; Sato et al. 1995) during the menstrual cycle. As the hormonal and physiological changes throughout the menstrual cycle follow a complex and continuous pattern that cannot be characterized by two or four sampling points, experiments with a higher time resolution were required. Daytime, pre-measurement conditions and the laboratory situation substantially affect cardiac autonomic regulation and might be the reason for some inconsistencies between previous studies. The aim of the present study was to investigate changes in RSA during the menstrual cycle in healthy subjects. For this purpose, daily beat-to-beat HR recordings were performed by the women themselves under basal conditions (morning) at home (thus avoiding an additional effect of the laboratory situation) with standardized pre-measurement history (sleep).

Methods

Subjects

26 women [mean (SD) age 23.4 (2.1) years, range 20–29 years] participated in this study. They were all healthy non-smokers, had regular menstrual cycles with an average length of 24–30 days in the preceding 5 months and had not used oral contraceptives for at least 5 months prior to the study. The length of the menstrual cycles during the study period ranged from 23 to 35 days [mean (SD) 27.9 (2.6) days]. All but one of the subjects were students from the local university. In five subjects data from only one cycle were available either because of absence of ovulation or for family or work reasons. Thus, the final evaluation was performed with data from 47 cycles of 26 subjects. Informed consent to participate was obtained from every subject. They were free to leave the study at any time. The experimental protocol was approved by the Ethics Committee of the University of Graz.

Experimental procedures

Beat-to-beat HR was recorded during two consecutive menstrual cycles from chest-wall electrocardiography leads every morning at the same time (± 1 h) before getting up. Microprocessor-based solid-state recorders (HeartMan, Institute of Physiology, University of Graz, Austria) with analog R-wave detection (resolution: 0.1 ms on average, 1 ms worst case) were used for R–R interval recording. Each subject was equipped with a portable data recorder and instructed on its use. Measurements started 2–3 days before the next menstrual period. Recordings were taken for 10 min daily while subjects were lying supine at rest and breathing spontaneously. Ovulation was determined using ovulation predictor kits (Selfcare, New Jersey, USA), which identify luteinizing hormone in urine. The day after a positive test result was taken to be the day of ovulation. Oral measurement of basal body temperature was performed daily.

Data analysis

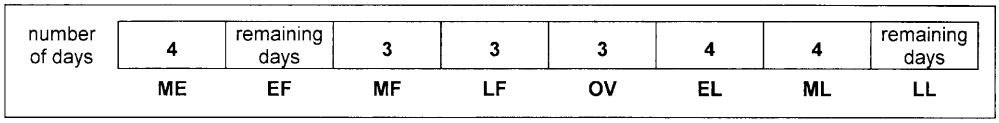
R–R intervals were converted to HR. Median HR values were calculated for each 10-min rest period. HRV was analyzed using a time-domain method, as described by Moser et al. (1998), in which absolute HR differences (in beats/min) from one heart beat to the next were calculated for the whole 10-min period. We used the median of these absolute beat-to-beat differences. Taking the logarithm of this median (logRSA) results in an approximately normal distribution of intra- and inter-individual values. This measure was chosen due to its robustness and insensitivity to outliers and ectopic beats, as well as due to its desirable statistical properties. Moreover, in our experience, logRSA is well suited for long-term studies and especially for self-measurements of HRV (Lehofer et al. 1997; Lehofer et al. 1999; Moser et al. 1994, 1998; Strauss-Blasche et al. 2000). LogRSA reflects fast (vagal) components of HRV but not slow ones originating from combined sympathetic and parasympathetic activity. This method was originally described by Eckoldt (1990) and modified by Moser et al. (1994, 1998). Respiratory frequency was estimated from the HF component of HRV using a method modified from Bettermann et al. (1996). This method uses linear band-pass filtering of HRV (Butterworth, order 20, cut-off frequencies 0.1 and 0.5 Hz) and counts respiratory cycles after removing eventual artifacts.

To compensate for inter- and intra-individual differences in cycle length and to simplify statistical analysis, each menstrual cycle was divided into eight phases, as described by Driver et al. (1996). As we could not observe differences between the first and the second menstrual cycle, all day-by-day values from a single subject were averaged within the 8 phases, and thereby the validity of each value for statistical analysis was enhanced (in 5 subjects values of only one cycle could be evaluated, in the remaining 21 subjects mean values were computed from the data of 2 cycles). The definition of the phases is illustrated in Fig. 1.

Statistical procedures

A repeated-measures analysis of variance (ANOVA) was performed, followed by least-squares difference (LSD) post-hoc tests between the individual phases of the menstrual cycle. LogRSA data were additionally compared using a two-way ANOVA for repeated

Fig. 1. Definition of the eight phases of the menstrual cycle. (*ME* menstruation, *EF* early follicular, *MF* mid-follicular, *LF* late follicular, *OV* ovulation – including the presumed day of ovulation in the middle, *EL* early luteal, *ML* mid-luteal, *LL* late luteal)



measurements (menstrual phase × subgroup), followed by LSD post-hoc tests. The individual coefficients of correlation between daily HR and logRSA values were Fischer's Z-transformed, averaged within the low HR and high HR groups and tested for significant difference between independent samples. A P value of less than 0.05 was considered to be significant.

Results

Data analysis derived from the entire collective revealed significant changes in HR during the menstrual cycle: the minimum was in the early follicular phase and the maximum in the late luteal phase (Fig. 2). LogRSA displayed no significant variation in the course of the menstrual cycle (Fig. 2). Respiratory frequency showed no change until the ovulatory phase, and then rose steadily through the early, mid- and late luteal phases (Fig. 2). Basal body temperature showed the well-known increase during the luteal phase (Fig. 2).

During inspection of individual curves it became apparent that the time course of logRSA fluctuations during the menstrual cycle differed between individuals, obviously depending on average HR. The individual minima and maxima of logRSA values during the menstrual cycle occurred mainly in the early follicular or mid-luteal phase. We calculated the difference between these two extreme points (ΔlogRSA; mid-luteal minus early follicular phase) and correlated this difference with the average HR (Fig. 3). A significant negative correlation was found ($r = -0.64$, $P < 0.001$), indicating that the changes of logRSA during the menstrual cycle shifted from an increase (logRSA higher in the luteal phase, positive values) to a decrease (logRSA higher in the follicular phase, negative values) with increasing HR (Fig. 3). Therefore the subjects were divided into three groups according to their average HR: low, medium and high HR groups (< 60 beats/min, 60–67 beats/min and > 67 beats/min, referred to as LHR, MHR and HHR groups, respectively). In all three groups the time course of changes in HR (Fig. 4, top graph) and basal body temperature (not shown) during the menstrual cycle remained similar in the entire collective (Fig. 2). However, the time course of logRSA fluctuations differed distinctively between groups: logRSA was higher during the luteal compared to the follicular phase in the LHR group, but the trend was reversed in the HHR group (Fig. 4, bottom graph). The MHR group showed no significant fluctuations of logRSA during the menstrual cycle. Table 1 summarizes mean (SEM) values of age, HR, logRSA, respiratory frequency and basal body temperature in the three groups. There were no significant differences in all parameters except HR between the groups.

We analyzed the relationship between daily HR and logRSA values in the HHR and LHR groups. Strong negative correlations were observed in the HHR group (mean $r = -0.74$, Fig. 5, top graph). Individual coefficients of correlation were all negative and significant. On the contrary, in the LHR group there were mainly weak positive correlations (mean $r = 0.13$, Fig. 5, bottom graph; $P < 0.001$ for difference between groups), with significantly positive coefficients of correlation in two women, whereas in the remaining seven the correlations were not significant.

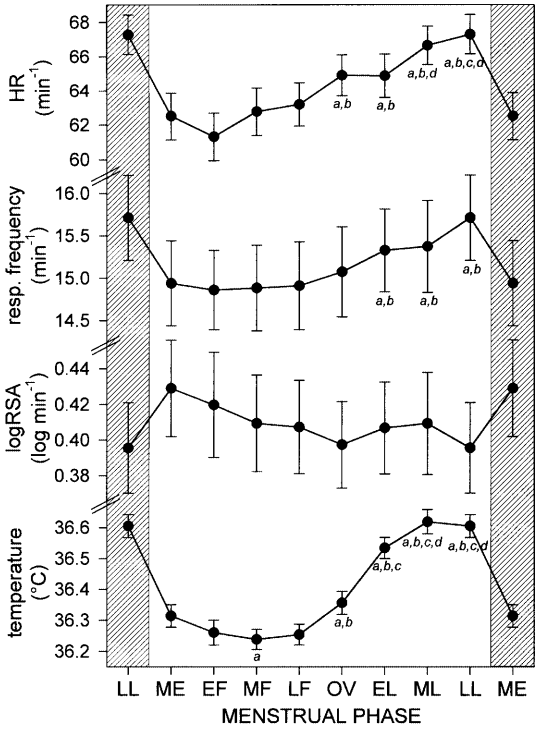


Fig. 2. Heart rate (*HR*), respiratory (*resp.*) frequency, time-domain measure of respiratory sinus arrhythmia (*logRSA*) and basal body temperature during the eight phases of the menstrual cycle [mean values (SEM)] of all subjects ($n = 26$). To emphasize the cyclic pattern, the first and the last menstrual phase (ME and LL) are plotted twice (*shaded areas*). [a]Significantly different from menstrual phase (ME); [b]significantly different from all follicular phases (EF, MF, LF), [c]significantly different from ovulatory phase (OV), [d]significantly different from early luteal phase (EL)

Discussion

The present study was designed to characterize changes in cardiac vagal control during the menstrual cycle by

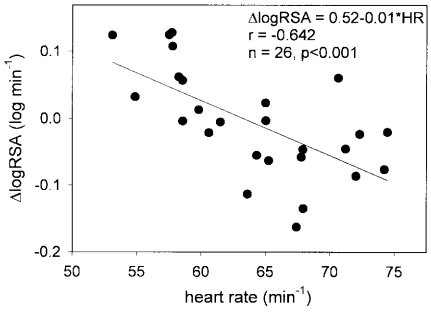


Fig. 3. Difference between the extreme values of logRSA (Δ*logRSA*; ML minus EF phase) as a function of average HR in 26 subjects

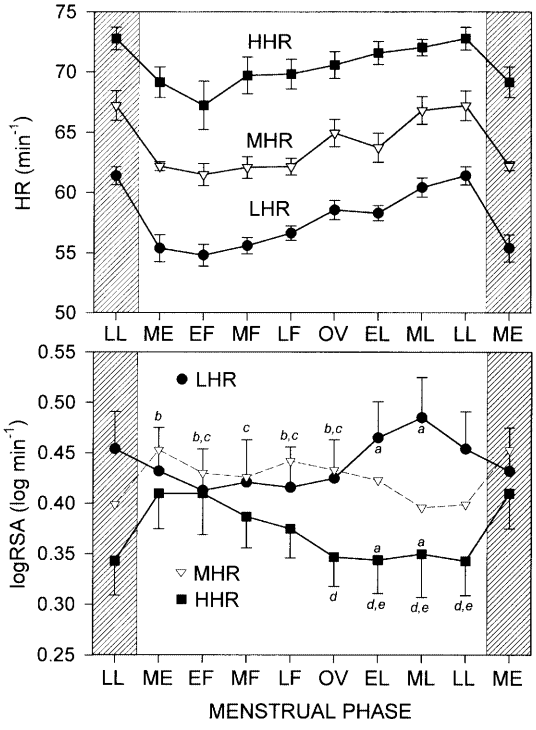


Fig. 4. Heart rate during the eight phases of the menstrual cycle [top graph; data are presented as mean (SEM)] averaged separately for the high HR group (*HHR*; $n=10$), the medium HR group (*MHR*; $n=7$) and the low HR group (*LHR*; $n=9$). Significant differences between menstrual phases are not shown. Shown on the bottom graph is logRSA at the eight phases of the menstrual cycle [mean (SEM)] averaged separately for the HHR ($n=10$), MHR ($n=7$) and LHR ($n=9$) groups. For better clarity and comprehensibility, error bars in the MHR group are not plotted (no significant differences between menstrual phases). [a]Significant difference between HHR and LHR group; [b]significantly different from EL phase; [c]significantly different from ML phase, [d]significantly different from ME phase, [e]significantly different from EF phase

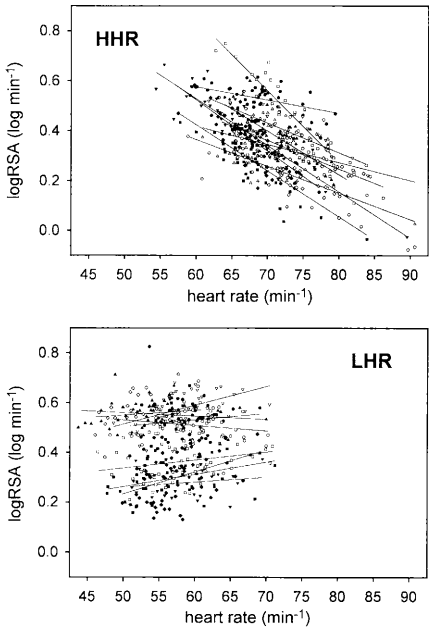


Fig. 5. Linear correlation between daily values of HR and logRSA within the individual women of the HHR group (top graph) and the LHR group (bottom graph)

measuring HRV. We used a portable beat-to-beat HR recorder for daily self-measurements performed by the subjects at home immediately after waking up in the morning. Thus, they can be considered as basal values, avoiding laboratory situations. Pre-measurement conditions (sleep) were well standardized. This methodical approach provided more detailed information on changes of HR and RSA during the menstrual cycle than previous studies, in which only one measurement per week (Saeki et al. 1997) or one for each half of the menstrual cycle (Guasti et al. 1999; Sato et al. 1995) was carried out.

The main finding of the present study was that the time course of the fluctuations of RSA during the menstrual cycle differed between individuals depending on their average HR. Changes in logRSA during the menstrual cycle shifted from positive (logRSA higher in the luteal phase) to negative (logRSA higher in the follicular phase) values with increasing HR (Fig. 3). The division of the subjects into three groups according to their average HR (HHR, MHR and LHR groups) allowed us to characterize the different patterns of vagal regulation during the menstrual cycle. An opposing time course of RSA fluctuations was found in the HHR compared to the LHR group (Fig. 4). During the follicular phase, logRSA was higher compared to the luteal phase in the HHR group, whereas it was lower in the LHR group. The MHR group showed no significant change of logRSA during the menstrual cycle and therefore represents an intermediate between the LHR and HHR groups; this was also the case with the time

Table 1. Physiological characteristics of subjects divided into three groups according to their average heart rate. Data are presented as the mean (SEM). (*LHR* low heart rate, *MHR* medium heart rate, *HHR* high heart rate)

Parameter	LHR ($n=9$)	MHR ($n=7$)	HHR ($n=10$)	All subjects ($n=26$)
Age (years)	23.8 (0.7)	22.0 (0.7)	24.0 (0.6)	23.4 (0.4)
Heart rate (beats/min)	57.4 (0.7)**	63.6 (0.7)	70.6 (0.9)*,**	64.3 (1.2)
logRSA (log/min)	0.44 (0.00)	0.42 (0.10)	0.37 (0.00)	0.42 (0.00)
Respiratory frequency (breaths/min)	14.5 (0.7)	15.9 (1.2)	15.2 (0.9)	15.14 (0.5)
Basal body temperature (°C)	36.39 (0.1)	36.38 (0.1)	36.43 (0.1)	36.41 (0.0)

*LHR vs. HHR, $P<0.001$; **MHR vs. LHR and HHR, $P<0.01$

course of changes in RSA. Interestingly, regardless of these differences in RSA fluctuations, the time course of HR was similar in all three groups (Fig. 4). These HR changes during the menstrual cycle (minimum in the early follicular phase, maximum in the late luteal phase) are in accordance with two published studies in which daily morning measurements of average HR (but not HRV) were performed (Döring and Feustel 1953; Manhem and Jern 1994).

Recently, the R–R interval was found to be the most suitable index for sympathovagal balance (Goldberger 1999). In the study presented here, changes in the R–R interval (the reciprocal value of HR) between minimal values in the early follicular and maximal values in the late luteal phase were not different between the LHR and HHR groups [–119 (16) ms for LHR, –74 (26) ms for HHR]. Therefore, shifts in sympathovagal balance during the menstrual cycle were comparable between groups. It is possible that in the LHR group a greater increase in sympathetic activity occurred during the luteal phase than in the HHR group, as it was opposed by vagal increase (increase in logRSA), but resulted in the same R–R interval increase across the menstrual cycle. Thus, in the HHR group, opposing changes of the sympathetic and parasympathetic nervous system occurred, whereas in the LHR group there was a parallel activation of both autonomic branches in the luteal phase of the menstrual cycle. This different interplay of both parts of the autonomic nervous system is further documented by differences in the relationship between daily HR and logRSA values (Fig. 5). In the HHR group, logRSA decreased with increasing HR, the negative correlation being highly significant, whereas in the LHR group, weak positive correlations were found.

Some studies indicate that RSA is influenced by respiratory rate and tidal volume (Berntson et al. 1997; Brown et al. 1993; Hirsch and Bishop 1981). Therefore, we analyzed whether different changes of respiratory rate during the menstrual cycle between the groups could account for the observed differences in RSA fluctuations. We found an increased respiratory frequency toward the end of the menstrual cycle in the group as a whole (Fig. 2). The most prominent changes of respiratory frequency during the menstrual cycle were observed in the MHR group, which did not show any change in RSA. The average respiratory frequency did not differ between groups (Table 1). We therefore conclude that the small changes in respiratory frequency observed during the menstrual cycle are not responsible for the significant differences in RSA fluctuations observed between the LHR and the HHR group. It was not possible to measure tidal volume with reasonable efforts within our experimental setting, which might be a limitation of the study because tidal volume has been reported to change during the menstrual cycle (Das 1998).

Previous investigations analyzing RSA during the menstrual cycle are in line with our data recorded from the HHR group. Two studies comparing the two halves of the menstrual cycle found a significantly increased RSA in the follicular phase compared to the luteal phase (Guasti et al. 1999; Sato et al. 1995). Although Saeki et al. (1997) reported higher values in the follicular phase too, their results were only significant in comparison to the menstrual phase. We found similar results in the HHR group with comparable HR values to the groups investigated by Guasti et al. (1999). In contrast, Sato et al. (1995) reported only that there were no significant changes in HR during the menstrual cycle, while Saeki et al. (1997) presented results on HRV only, unfortunately without mentioning the HR values. Our measurements were performed in the early morning close to the daily minimum in HR usually observed at 3 a.m. Other studies recorded HR later during the day (Guasti et al. 1999) or did not report the time of measurement (Saeki et al. 1997; Sato et al. 1995). As there are circadian fluctuations of autonomic activity, these differences in the time of measurement during the day could be responsible for the divergent results.

Our subjects were interviewed about their fitness level and their training activities: none of the subjects were top-performance athletes, and those who engaged in leisure-time physical activities were equally represented in each of the HR groups, in spite of the known relationship between physical fitness and low resting HR.

As different types of cardiac vagal regulation were most evident in the luteal phase of the menstrual cycle, several questions arise: (1) Is there a relationship between the occurrence of premenstrual syndrome (PMS), which is associated with symptoms of autonomic disturbance, and the average HR of a woman? (2) Do different types of vagal regulation also exist during pregnancy? (3) What are the implications for the course of pregnancy? With regard to the first question, none of our subjects complained about severe PMS. Studying women with PMS would possibly elucidate the underlying factors of this epidemiologically important field of women's health. During pregnancy, women are at risk of autonomic dysfunction, which is reflected in the occurrence of diseases like emesis gravidarum or preeclampsia. And in relation to questions (2) and (3), in our laboratory we are currently performing daily beat-to-beat morning measurements of HR during early pregnancy.

In conclusion, we observed significant changes in HR during the menstrual cycle that were independent of the individual average HR. In contrast, amplitudes of change of logRSA as an index of cardiac vagal control were found to correlate with HR. High and low HR groups displayed opposing trends throughout the course of the menstrual cycle. Possibly the high time resolution (daily measurements), the time of day of our recordings (morning) and the standardized pre-measurement conditions (sleep) are of importance in detecting inter-individual differences in cardiac parasympathetic regulation during the menstrual cycle. Future studies will have to address the question of whether individual differences in cardiac vagal control during the menstrual cycle mirror

the susceptibility to PMS as well as autonomically mediated diseases during pregnancy.

Acknowledgements We greatly acknowledge the cooperation of the women who took part in this study. The authors wish to thank Dietmar Messerschmidt, Graz, Austria, for technical support, and the late Prof. Dr. Gunther Hildebrandt, Marburg, Germany, Philip J. Kilner, London, UK, Prof. Dr. Abraham Noordergraaf, Pennsylvania, USA, and Dr. Daniel McLeod, Baltimore, USA for valuable contributions. This study was supported by the Anniversary Fund of the Austrian National Bank (project number 6203) and by the special research project "Optimization and Control" (part 312) of the Austrian Research Fund.

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