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REVIEW

Impact of endogenous and exogenous progesterone exposure on stress biomarkers: a systematic review

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ABSTRACT

Stress activates the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis (HPAA). Based on a systematic literature review of the impact of endogenous and exogenous exposure with natural progesterone on the stress response in healthy premenopausal and postmenopausal women, the following conclusions can be drawn: the HPAA activity was not relevantly affected by endogenous progesterone exposure across the menstrual cycle, but might be reduced by exogenous micronized progesterone application; in contrast, the ANS has a sympathetic predominance in the (progesterone-dominated) luteal phase of the menstrual cycle. Future studies should assess various stress biomarkers under various hormonal conditions to, for example, allow for cardiovascular risk stratification in hormone users.

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Heart rate variability; hypothalamic–pituitary–adrenal axis; cortisol; progesterone; menstrual cycle; menopause; menopausal hormone therapy

Introduction

Stress is the body's response to intrinsic or extrinsic positive or negative challenging factors. Acute stress reactions last for minutes or hours, whereas chronic stress is defined as maladjustment to repeatedly occurring stressors due to the absence of appropriate coping mechanisms[1] lasting for days to months[2]. Stressors activate the autonomic nervous system (ANS) and hypothalamic–pituitary–adrenal axis (HPAA)[3].

Non-invasive measurement of heart rate variability (HRV) – that is, the ongoing beat-to-beat variation of cyclic heart activity[4] – is an established method to assess the autonomic balance[5] and to characterize ANS reactivity[6]. Reduced HRV implies less ANS adaptability and has been found to be associated with increased cardiovascular disease morbidity[7] and mortality[8]. Both elevated sympathetic and decreased parasympathetic activity tend to aggravate arrhythmias leading to death[9]. There are two common ways to measure HRV: time domain analysis and frequency domain analysis (Tables 1 and 2)[10].

Cortisol is the executive hormone after HPAA stimulation aiming to provide sufficient energy to overcome stress factors[11] by, for example, encouraging catabolic pathways as proteolysis and lipolysis, raising plasma concentrations of glucose, free fatty acid, and insulin[12], and modulating the immune system[13]. Cortisol levels can be measured in plasma, serum, saliva, and urine. The unbound cortisol fraction represents the physiological reactive cortisol amount. Unbound salivary and urinary cortisol levels are strongly correlated and better represent adrenocortical function than the total cortisol serum level, which mainly represents protein-bound cortisol[11,14]. In contrast, approximately only 14% of salivary and 1% of urinary cortisol is protein bound[11].

Especially, chronic stress exposure is associated with an increased risk for several chronic non-communicable diseases such as cardiovascular diseases[15], gastrointestinal diseases[16], diabetes mellitus, osteoporosis, immunodeficiency[17], sleeping disorders[18], and chronic pain[19]. In women, the non-communicable disease risk also increases after menopause and may be attenuated or even prevented by menopausal hormone therapy (MHT)[20]. Indeed, endogenous sex hormones have been shown to have an impact on the ANS[21–23] and the HPAA[24]. Similarly, in postmenopausal women MHT has been found to beneficially modify the stress response[22,25].

The aim of this systematic review was to investigate the impact of endogenous (menstrual cycle) and exogenous (MHT containing micronized progesterone [MP]) progesterone (P) exposure on stress biomarkers, cortisol, and HRV, respectively.

Materials and methods

In November 2018, a systematic literature search was performed using the Medline database (PubMed). Only articles in English and studies in humans were included.

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Supplemental data for this article can be accessed here.

Table 1. Selected time domain parameters of heart rate variability.

Parameter (unit)	*Description*
SDNN (ms)	Standard deviation of all normal sinus beat intervals[9]; representing the balance of sympathetic and parasympathetic activity, a reduction implies a diminished vagal activity[61]
SDANN (ms)	Standard deviation of the averages of normal sinus beat intervals in all 5-min segments along the whole electrocardiogram recording[9]
SDNN index (ms)	Mean of the standard deviations of all normal sinus beat intervals for all 5-min segments along the whole electrocardiogram recording[9]
RMSSD (ms)	The square root of the mean of the sum of the squared differences between adjoining normal sinus beat intervals[9]; reflecting the parasympathetic part of autonomic nervous system[61]
NN50 count	Number of pairs of adjoining normal sinus beat intervals deviating by more than 50 ms along the whole recording[9]
pNN50 (%)	NN50 count divided by the total number of all normal sinus beat intervals[9]; reflecting the parasympathetic part of autonomic nervous system[61]

Table 2. Selected frequency domain parameters of heart rate variability.

Parameter (unit)	*Description*
ULF (ms^2)	Power in ultra-low-frequency spectrum ($\leq$0.003 Hz)[9]
VLF (ms^2)	Power in very-low-frequency spectrum (0.003–0.04 Hz)[9]
LF (ms^2)	Power in low-frequency spectrum (0.04–0.15 Hz)[9]; representing the sympathetic and parasympathetic influence[62]
LF norm (n.u.)	Low-frequency power in normalized units[9]
HF (ms^2)	Power in high-frequency spectrum (0.15–0.4 Hz); representing the impact of parasympathetic part on the autonomic nervous system[62]
HF norm (n.u.)	High-frequency power in normalized units[9]
LF/HF ratio	Representing balance of sympathetic and parasympathetic activity[63]
Total power (ms^2)	Variance of all normal sinus beat intervals (approximately $\leq$0.4 Hz)[9]; reflecting the complete activity of the autonomic nervous system[62]

As MP has been available in Europe since 1980[26] and worldwide since 1986[27], only articles published after 1980 were included. For each topic – that is, impact of endogenous P and exogenous MP on the HPAA and HRV – individual searches were performed using multiple combinations of keywords, Mesh terms, and text words related to the respective topic. For the first topic, included keywords were the MeSH terms 'corticotropin-releasing hormone', 'adrenocorticotropic hormone', and 'cortisol' and its keywords using the logical connection OR. The resulting hits were connected to the MeSH terms 'progesterone', 'hormone replacement therapy', and 'menstrual cycle' and its keywords using the logical connection AND. To restrict the number of hits to those with the highest scientific evidence level, only meta-analyses, systematic reviews, and randomized controlled trials (RCTs) were included. For the second topic, the MeSH terms 'heart rate variability' were linked with 'progesterone', 'hormone replacement therapy', and 'menstrual cycle' and its keywords using the logical connection AND. Assuming that the review by von Holzen *et al.*[22] was complete, only articles published after 2015 were considered for all search commands with 'heart rate variability'. Exclusion criteria were other medications expected for MHT not containing MP that may influence the HPA or the ANS, respectively. Similarly studies without clear identification of progestogen type were excluded.

Results

Out of 321 hits, 41 articles fulfilled the inclusion and exclusion criteria and were included in the review (Table 3).

Impact of progesterone on the hypothalamic–pituitary–adrenal axis

Impact of endogenous progesterone exposure across the menstrual cycle on the hypothalamic–pituitary–adrenal axis

Overall, 19 studies evaluated the impact of endogenous P exposure across the menstrual cycle on the HPAA[3,14,28–44] (Supplementary Table S1). Of those, 12 studies assessed baseline HPAA serum level[3,14,29,31–34,36–38,40,43], and 12 studies assessed HPAA reactivity after a challenge test[3,14,28–30,35,36,39,41–44]. All but three articles were RCTs, while two were systematic reviews[31,43] and one was an observational cohort study[3]. The sample size ranged from five[35] to 56[29] subjects. Mean age ranged from 20.7 years[38] to 36.6 years[42], or was not clearly specified[29,44]. Participants were neither pregnant nor users of hormonal contraceptives and were generally healthy in all but two studies including women with premenstrual syndrome (PMS)[36,43] or premenstrual dysphoric disorder (PMDD)[42], respectively. One study did not report subjects' health condition[34].

Assessments of the baseline HPAA serum level comprised at least one cortisol serum sample during the follicular phase and another during the luteal phase of the menstrual cycle in most studies[30,32,33,35,36,39–44]. Others used salivary cortisol[28,29,33,34,37,43], urinary cortisol[14,38,43], adrenocorticotropic hormone (ACTH) serum[30,43], or corticotropin-releasing hormone (CRH) samples[31], respectively. Cortisol levels were measured by various methods including radioimmunoassay[14,30,32,38–42,44], enzyme immunoassay[3,28,29,33,37], chemiluminescent immunoassay[33,35], time-resolved fluorometric immunoassay[34], and solid-phase fluoroimmunoassay[36]. ACTH and cortisol samples were mostly taken between 6:00 a.m. and 12:30 p.m.[3,14,32,33,35,38,40,41,44], and others either in the afternoon between 1:00 and 8:00 p.m.[28–30,37,38] or along

Table 3. Literature search.

	HPAA AND progesterone	HPAA AND menstrual cycle	HPAA AND HRT	HRV AND progesterone	HRV AND menstrual cycle	HRV AND HRT
Hits (*n*)	137	81	72	5	21	5
Included articles (*n*)	7	19	2	1	12	0

HPAA, hypothalamic–pituitary–adrenal axis; HRT, hormone replacement therapy; HRV, heart rate variability.

the entire day[34,38]. The remaining studies did not describe the exact time point of cortisol[31,32,36,39,42,43] or CRH[31] sample collection.

While CRH secretion has been reported to change across the menstrual cycle displaying a CRH[31] or ACTH[45] peak, respectively, around the time of ovulation, the majority of studies did not observe a change of baseline cortisol serum[3,14,32–34,36,38,40,43], salivary[14,34,38], and urinary[14,38] levels across the menstrual cycle. These findings support the earlier systematic review from 1994[43] showing no impact of the menstrual cycle on basal serum cortisol[46–51] and serum ACTH levels[52]. Some studies also showed no difference for the menstrual cycle on basal urinary[53] and serum[45,54] cortisol levels[55] in women with PMS. However, others found higher salivary[29] and serum cortisol levels during the luteal than follicular phase, or vice versa for salivary[33,37] 24-h urinary cortisol[38]. When comparing women with and without PMDD, the mean values of serum cortisol levels were higher during the follicular phase in women with PMDD and higher in the luteal phase in controls[40].

Twelve studies investigated the HPAA responsiveness to a challenge test in relation to the menstrual cycle and yielded conflicting results[3,14,28–30,35,36,39,41–44].

In detail, five studies did not report any alterations in HPAA responsiveness due to the menstrual cycle on urinary[14], salivary[14], and serum cortisol[30,35,41,44] and serum ACTH levels[30]. In these studies, the following HPAA challenge tests were applied: insulin tolerance test[30], physical exercise[14,35], alcohol drink[41], and different diets[44]. These findings support the earlier systematic review from 1994[43] showing no impact of the menstrual cycle on serum cortisol[53,56], serum ACTH[53], and urinary cortisol[57] responsiveness. The HPAA challenge tests used were intravenous ovine CRH injection[53], psychoneuroendocrine stress[57], and physical exercise[56].

In contrast, others reported a higher salivary[28] and serum[39] cortisol stress response in the follicular phase as compared to the luteal phase. In these studies, the Trier Social Stress Test[28], intravenous alcohol injection[36], an alcohol drink[42], or a certain diet[39] were used as HPAA challenge tests.

Quite the opposite was observed by two studies[29,39] using either a cold pressor stress test[29] or soy diet[39] as the HPAA challenge test, respectively. They found a higher salivary[29] and serum[39] cortisol stress response in the luteal phase as compared to the follicular phase.

Bringing up one study in particular, Ohara *et al.*[3] compared salivary cortisol levels at baseline and after a 14-h fast (fasting trial), respectively, after a 12-h fast followed by a meal intake (meal intake trial) affected by menstrual cycle phases. The data analysis showed higher baseline cortisol levels in the luteal phase and different phase-related enhancement dependent on the time point of sample collection in the fasting trial. On the contrary, there no alteration of baseline cortisol concentration was detected in relation to cycle phases in the meal intake trial and higher cortisol levels after meal intake in all cortisol measurements. Worthy of note, all data for this publication were not statistically analyzed, as they were only mentioned as values in graphics[3].

Impact of MHT containing micronized progesterone on the hypothalamic–pituitary–adrenal axis

Overall, only two RCTs investigated the impact of MHT containing MP on the HPAA in healthy postmenopausal women[58,59] (Supplementary Table S2). The sample size ranged from 10[58] to 25[59] participants, and mean age from 54.8 years[58] to 57.5 years[59], respectively. In both trials, interventions comprised a continuous combined MHT regimen containing standard-dose estrogens (transdermal estradiol at 50 μg/day[58,59], oral conjugated equine estrogens at 0.625 mg/day[59]) and oral MP at 100 mg/day[58,59]. The duration of the intervention ranged from 12 weeks[59] to 12 months[58]. Basal morning cortisol serum samples were analyzed by radioimmunoassay at baseline and after 1 month[58], 3 months[58,59], 6 months, 9 months, and 12 months[58], respectively. Compared to baseline, short-term MHT (3 months) did not alter basal cortisol serum concentrations[59], while 6 months of MHT significantly reduced basal cortisol serum concentrations[58].

Impact of progesterone on heart rate variability

Impact of endogenous progesterone exposure across the menstrual cycle on heart rate variability

Of 21 hits, 12 studies evaluated the impact of endogenous P exposure across the menstrual cycle on HRV[3,6,10,21,22,60–66] (Supplementary Table S3). There were one systematic review[22], one RCT[62], seven prospective observational cohort studies[3,6,10,61,64–66] and three comparative analyses[21,60,63].

Sample size ranged from 7[3] to 100[21] participants, and mean age from 19.2 years[66] to 48.8 years[64] or age range from 18 to 37 years[10,21,61], respectively. Women were generally healthy and neither pregnant nor users of hormonal contraception. One study compared perimenopausal women with and without insomnia[64], one study included women with mild PMS[66], and one study did not report subjects' health condition[6]. For inclusion into this review, HRV assessment had to be performed at least once during the follicular phase and once during the luteal phase of the menstrual cycle. The majority of studies recorded HRV parameters for several minutes[3,10,21,60,62–64,66], while three performed 24-h electrocardiogram recordings[6,61,65] or analyzed multiple time points during different sleep stages[64].

The first systematic review from 2016 analyzed 15 studies on cardiac autonomic control with respect to the menstrual

cycle[22]. Qualitative comparisons between the vast majority of studies demonstrated a decrease of the vagal dominance on the heart from the follicular to the luteal cycle phase.

More recent studies reported comparable results showing overall a predominance of sympathetic activity in the luteal phase[3,6,10,21,60,61,66] and predominance of parasympathetic activity in the follicular phase[10,60], respectively. These findings were in the majority independent of the subject's position (supine, seated, standing)[60]. Sleep deprivation has been found to have an impact on cardiac autonomic control, displaying a move to a predominance of parasympathetic activity after ovulation and a predominance of sympathetic activity before ovulation[63].

However, others did not find any significant differences in cardiac autonomic control between different menstrual cycle phases[62,65].

Impact of MHT containing micronized progesterone on heart rate variability

So far, there have not been any studies investigating the impact of MHT containing estrogens combined with MP on HRV.

Discussion

Stress activates the ANS and the HPAA. Sexual steroid hormones have been found to modulate the stress response. The aim of this systematic review was to specifically analyze the impact of endogenous and exogenous exposure with natural P on the stress response. Our systematic review revealed that the HPAA activity was not relevantly affected by endogenous P exposure across the menstrual cycle, but might be reduced by exogenous MP application. In contrast, the ANS has a sympathetic predominance in the (P-dominated) luteal phase and parasympathetic predominance in the follicular phase of the menstrual cycle, but has not yet been evaluated under exogenous MP exposure.

Most studies did not observe an impact of endogenous P exposure on baseline[14,32–34,36,38,40,43,46–53,55] or stimulated[14,30,35,41,43,44,53,56,57] HPAA. However, few studies reported higher baseline[33,37,38] and stimulated[28,36,39] cortisol levels during the follicular phase, or vice versa[3,29,39,45,54]. Varying results may be due to the type of specimen analyzed (serum, saliva, urine) as differing results have been reported when comparing salivary (no change) to 24-h urinary (higher in the follicular phase) cortisol levels[38], or salivary (higher in the follicular phase) to serum (no change) cortisol levels[33], respectively. As cortisol is secreted in a circadian pattern, the time point of sampling is crucial. For example, serum cortisol levels have been found in a previous study to be higher during the follicular phase than the luteal phase when comparing samples taken at 8:00 a.m., while there was no difference when comparing 3:00 p.m. samples across the cycle[67]. The studies included in this review had a wide time spectrum for sampling, or did not even mention it[31,36,39,42,43]. Furthermore, as the individual menstrual cycle length varies[43], a defined cycle day for (serum, saliva, urine) sampling may still yield different interpersonal and intrapersonal results. Serum cortisol levels are also affected by other factors such as cortisol binding globulin serum levels or comorbidities such as diabetes mellitus[68] and mood disorders[69]. Women recruited for the studies were characterized to be healthy in general, yet differences in medication, body weight, and lifestyle factors (physical activity, alcohol, diet) and sleeping patterns that physiologically change across the menstrual cycle may affect the stress response[6]. Finally, a broad range of different methods to analyze cortisol levels was applied. Two studies[58,59] evaluated the impact of MHT containing oral MP on the HPAA, with long-term MHT reducing basal serum cortisol levels. Besides duration of MHT application, other factors such as estrogen type (estradiol, conjugated equine estrogens) and mode of application (oral, transdermal) may yield different results. Importantly, MP was not studied as monotherapy but only in combination with estrogens; thus, differentiating between the two sex steroids' impact on cortisol levels was impossible.

With respect to ANS control, most studies reported a parasympathetic dominance in the follicular phase or a sympathetic dominance in the luteal phase of the menstrual cycle[6,10,21,60,61,63,64,66,70–81]. This supports previous findings of an increased prevalence of arrhythmias during the luteal cycle phase[82]. Contradictory results by others might have been due to certain study designs, for example sleep deprivation[63], or cohorts either differentiating between women with and without PMS[72,76,77,80,81] or not[70,71,73–75,78,79,83–85]. Direct comparisons between studies were also impaired by different HRV assessment methods including varying duration and time point of electrocardiogram recording. So far, no study has reported the impact of MHT containing MP or MP alone on HRV. As previous studies have reported a beneficial effect of MHT on the stress response in postmenopausal women[22], which was even more pronounced with combined MHT than estrogen-only therapy[25], we would expect a shift to a vagal tonus at least for MHT combined with MP.

The strength of our review is the systematic literature search differentiating between two stress biomarkers (HPAA, HRV), and between endogenous and exogenous sex steroid hormone exposure, and restriction to truly natural P exposure. Clearly, our review also has some limitations such as restriction to publications in English, and identification of studies with only small sample sizes and mainly healthy women. Thus, results might be different in bigger cohorts and cannot be transferred to, for example, diseased individuals. Moreover, some data are mentioned without proof for significance[3,33,39,42,60]. Finally, the results out of our review cannot only be attributed to P itself, as the luteal phase is characterized by high levels of both steroid hormones, estradiol and P[43]. Most interestingly, there have so far been no studies combining the assessment of both stress biomarkers across the menstrual cycle or when applying MHT, respectively. In future, to obtain a broader picture of the impact of steroid sex hormones on the stress response, it would be preferable to assess various stress biomarkers at the same time (e.g. questionnaires, basal and stimulated serum and

salivary HPAA effectors, HRV under various conditions) to also evaluate their relative impact.

Conclusion

Stress activates the ANS and the HPAA. Our systematic review revealed that the HPAA activity was not relevantly affected by endogenous P exposure across the menstrual cycle, but might be reduced by exogenous MP application. In contrast, the ANS has a sympathetic predominance in the (P-dominated) luteal phase of the menstrual cycle. Future studies should assess various stress biomarkers under various hormonal conditions to, for example, allow for cardiovascular disease risk stratification in hormone users.

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