Sleep, rhythms and women’s mood. Part I. Menstrual cycle, pregnancy and postpartum

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Summary This review summarizes studies of sleep and other biological rhythms during the menstrual cycle, pregnancy and the postpartum period, focusing, where feasible, on studies in women who met DSM-IV (Diagnostic and Statistical Manual for Mental Disorders, 4th edition) criteria for a depressive disorder compared with healthy controls. The aim was to review supporting evidence for the hypothesis that disruption of the normal temporal relationship between sleep and other biological rhythms such as melatonin, core body temperature, cortisol, thyroid stimulating hormone (TSH) or prolactin occurring during times of reproductive hormonal change precipitates depressive disorders in predisposed women. Treatment strategies, designed to correct these altered phase (timing) or amplitude abnormalities, thereby improve mood. Although there may be some common features to premenstrual, pregnancy and postpartum depressive disorders (e.g. elevated prolactin levels), a specific profile of sleep and biological rhythms distinguishes healthy from depressed women during each reproductive epoch. Further work is needed to characterize more fully the particular abnormalities associated with each reproductive state to identify common versus distinctive features for each diagnostic group. This information could serve as the basis for developing more targeted treatment strategies.

Introduction

Since studies of sleep in women across the life cycle have been summarized previously,1 this review focuses more on studies of objective measures of sleep and other biological rhythms in women with and without depressive disorders. In addition, we examine the effects of interventions with sleep therapies (wake therapy or sleep deprivation) on mood and biological rhythms. As most studies of circadian rhythms in mood disorders measure melatonin, cortisol (more circadian-dependent hormones), TSH and prolactin (more sleep-dependent hormones), our review summarizes studies primarily using these measures, highlighting those studies in which investigators document reproductive endocrine status. This review will not focus on estradiol, progesterone, follicle-stimulating hormone (FSH) or luteinizing hormone (LH), because most studies measured serum levels of these...
hormones only once daily, rather than obtaining circadian measures. As a basis for this review, we performed literature searches using MEDLINE via PubMed, the journal article database for the International Library of Medicine, using key words, and limiting the output to studies performed on humans, and written in English. We then categorized the studies by reproductive epoch (menstrual cycle, pregnancy, postpartum) and by clinical status (normal controls, depressed patients). Published studies that examined sleep in relationship to other biological rhythms in clearly defined diagnostic groups are limited. Nonetheless, certain patterns of pathogenic phase or amplitude relationships between component biological rhythms in depressed compared with healthy control women, such as delayed offset of morning melatonin secretion, are evident.

### Menstrual cycle studies

In studies of sleep during the menstrual cycle, investigators generally make measurements during menses (1-5 days after the onset of bleeding), the follicular phase (1-14 days after the onset of menses before ovulation when FSH is secreted from the pituitary, and the ovarian follicle is developing and secreting increasing doses of estrogen), at ovulation (during the LH surge, 12-14 days after menses in a 28-day cycle), the luteal phase (14-28 days after the onset of menses, after ovulation when the corpus luteum secretes progesterone) or the premenstrual, late luteal phase (7-10 days before the onset of menses, when estradiol and progesterone levels are declining) (see Fig. 1).

### Sleep studies in healthy women during the menstrual cycle

Using subjective sleep reports, Patkai et al.² reported that sleep duration in six healthy women...
over two menstrual cycles was longest (by 1 h) and most disturbed premenstrually (5 days preceding the onset of menses), and shortest at ovulation. Similarly, Billiard et al.\(^3\) and Sachs et al.\(^4\) reported case histories of two adolescent females whose periodic hypersomnia was associated with menstruation. These studies are limited by small sample sizes and lack objective measures of sleep, mood or reproductive hormones to define menstrual cycle phase.

Further research on objective sleep recordings in 13 healthy women\(^5\) indicated rapid eye movement (REM) sleep latency was significantly shorter during the luteal, compared with the follicular, menstrual cycle phase. Three of the subjects, however, were taking oral contraceptives, and the follicular and luteal phase measures, documented by salivary progesterone, were not randomized or sequential. Also, although there was an orientation to the sleep laboratory, no adaptation night was specified.

Driver et al.\(^6\) carefully examined subjective, objective and electroencephalogram (EEG) power density throughout one menstrual cycle (phase determined by temperature and hormonal measures) in nine healthy women without symptoms of premenstrual syndrome (PMS). No significant variations across the menstrual cycle in subjective mood and sleep quality ratings, or in objective measures of total sleep time, sleep efficiency, sleep latency, REM sleep or slow wave sleep were found. Spectral analysis of non-REM (NREM) sleep, however, showed a large variation in power density (14.25-15.0 Hz band of sleep spindles) across the menstrual cycle, with a maximum in the luteal phase that paralleled core body temperature activity. In contrast, the time course of EEG slow wave activity (reflecting homeostatic sleep regulatory mechanisms) did not vary significantly across the menstrual cycle.

To exclude masking effects of light and behavior so as to investigate diurnal fluctuations of sleep propensity in the follicular and luteal phases, Shibui et al.\(^7\) conducted multiple nap tests using an ultra-short sleep-wake cycle in eight healthy women (20-23 years of age) without sleep disorders. Although there were no sleep differences between the two menstrual cycles from 17:00 to 08:30 h, daytime (09:00-16:30 h) subjective sleepiness and number of slow wave sleep-containing nap trials increased in the luteal compared with the follicular phase, suggesting a relation to mechanisms controlling slow wave sleep. Follicular and luteal menstrual phases were not documented by hormonal measures.

Sleep studies in women with mood symptoms during the menstrual cycle

Hartmann\(^8\) found that increased REM sleep (minutes and %) in the premenstrual period was correlated with severity of ‘premenstrual tension’ in four normal individuals and three inpatients with diagnoses that included depression and schizophrenia. Total sleep time and number of awakenings were unchanged; however, the fact that the subjects were taking medications, including oral contraceptives, Dexedrine and Prolixin, compromises the interpretation of findings from this study. While collecting sleep EEG data from four female students for eight nights over a single menstrual cycle, Cluydts and Visser\(^9\) found an increase in stage 2 and a decrease in delta sleep at the time of menses in the one subject who reported dysphoric mood premenstrually. Similarly, after adaptation to the sleep laboratory, Parry et al.\(^10\) examined sleep EEG, temperature and activity two nights per week over the course of one menstrual cycle in eight women with moderate to severe premenstrual depression (as defined by daily prospective ratings required for a DSM diagnosis and weekly Hamilton and Beck depression ratings), and eight age-matched controls. Depressed women had more stage 2 (%) sleep and less REM sleep (minutes and %) than healthy controls. Stage 3 sleep and number of intermittent awakenings, but not temperature or actigraphic wrist motor activity, varied with menstrual cycle phase. Lee et al.\(^5\) showed that women with premenstrual negative affect had significantly less delta sleep than asymptomatic women during both the follicular and luteal menstrual cycle phases, but these women had not been assessed by psychiatric interview using standardized diagnostic criteria for a depressive disorder. In contrast, Chuong et al.\(^11\) observed no significant polysomnographic (PSG) changes related to the menstrual cycle in nine sleep parameters or differences between three patients with premenstrual syndrome (PMS) (diagnosed by interview and a visual linear analog scale) and six control subjects studied for two consecutive nights during each of three menstrual cycle phases.

Summary

Although some studies suggest lighter, more disturbed sleep premenstrually and increased REM sleep and decreased REM latency in depressed patients, the marked inconsistency in the results of menstrual cycle sleep studies can be attributed
to variability of methods, small sample sizes, subjects on different medications, lack of hormonal measures to define menstrual cycle phase and no standardized criteria to determine depressive diagnosis (see Table 1).

Table 1  Sleep studies: menstrual cycle

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patkai et al. (1974)²</td>
<td>6</td>
<td>Subjective reports 2 MC</td>
<td>Sleep duration longest, most disturbed in PM; shortest at ovulation</td>
<td>No objective measures, mood reports or RH</td>
</tr>
<tr>
<td>Billiard et al. (1975)³</td>
<td>1</td>
<td>Case history, adolescent female</td>
<td>Periodic hypersomnia</td>
<td>Small N, subjective report, no RH</td>
</tr>
<tr>
<td>Sachs et al. (1982)⁴</td>
<td>1</td>
<td>PSG in F, L phases salivary P4</td>
<td>Y REM latency in L versus F phase; Y delta (%) both MC phases in W with NAS</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (1990)⁵</td>
<td>13</td>
<td>Ultra-short sleep wake cycle study in F, L phases</td>
<td>Y in L versus F phase; Y in L phase with ↑ Tc</td>
<td>No diagnostic criteria for NAS; 3 W on OC</td>
</tr>
<tr>
<td>Driver et al. (1996)⁶</td>
<td>9</td>
<td>PSG, EEG power density, subjective reports every 2nd night × 1 MC</td>
<td>↑ sleep spindles in L phase with ↑ Tc</td>
<td>Small N, no DP</td>
</tr>
<tr>
<td>Shibui et al. (2000)⁷</td>
<td>8</td>
<td>Inpatient PSG, mood ratings during MC</td>
<td>↑ REM (min, %) PM, correlated with mood</td>
<td>Inpatients on medications with mixed dx of depression and schizophrenia, no RH</td>
</tr>
<tr>
<td>Hartmann et al. (1966)⁸</td>
<td>3</td>
<td>PSG × 8 nights over 1 MC</td>
<td>↑ Stage 2 (%), ↓ delta (%)</td>
<td>1 subject reported dysphoric mood PM, no RH</td>
</tr>
<tr>
<td>Cluydts and Visser (1980)⁹</td>
<td>1 DP 3 NC</td>
<td>PSG × 8 nights over 1 MC</td>
<td>↑ Stage 2 (%), ↓ REM (min, %)</td>
<td>Hormonal measures not used to differentiate WK of MC</td>
</tr>
<tr>
<td>Parry et al. (1989)¹⁰</td>
<td>8</td>
<td>PSG, Tc, actigraphy</td>
<td>DP: ↑ Stage 2 (%) ↓ REM (min, %)</td>
<td></td>
</tr>
<tr>
<td>Chuong et al. (1997)¹¹</td>
<td>3</td>
<td>PSG 2 consecutive nights, 3 phases ×1 MC</td>
<td>No significant differences DP versus NC, same MC phase</td>
<td></td>
</tr>
</tbody>
</table>

DP, depressed patients; dx, diagnosis; EEG, electroencephalogram; F, follicular; L, luteal; MC, menstrual cycle; NAS, negative affect symptoms; NC, normal controls; OC, oral contraceptives; P4, progesterone; PM, premenses; PSG, polysonomography; REM, rapid eye movement; RH, reproductive hormones; SWS, slow wave sleep; Tc, core body temperature; W, women; WK, week.

Biological rhythm studies

Melatonin
In a study of healthy women, Nair et al.¹² found a phase-delay in the nocturnal peak of melatonin.
secretion during the mid-menstrual period (mid-cycle), although melatonin was sampled only every 2-4 h at two points in the cycle, and without documentation of estradiol or progesterone levels. In more extensive normal control studies, Brzezinski et al.\textsuperscript{13} (sampling every 2 h) and Berga and Yen\textsuperscript{14} (sampling every 30 min) found that melatonin circadian rhythms were relatively stable and resistant to hormonal influences during the menstrual cycle. Further work by Shibui et al.,\textsuperscript{15} who applied an ultra-short sleep-wake cycle schedule to eight healthy women, showed that the 24-h area under the curve of serum melatonin was significantly decreased in the luteal compared with the follicular menstrual cycle phase, suggesting a decrease in the pacemaker amplitude regulating the melatonin rhythm.

Sampling melatonin every 30 min, Parry et al.\textsuperscript{16} observed that, compared to eight normal control subjects, eight women who met DSM-IV\textsuperscript{17} criteria for premenstrual dysphoric disorder (PMDD) had an earlier (phase-advanced) offset of melatonin secretion, which contributed to a shorter secretion duration and a decreased area under the curve. Similar findings were seen in a larger follow-up study of 21 PMDD and 11 normal control subjects,\textsuperscript{18} where melatonin onset time was delayed, duration was compressed, and area under the curve, amplitude and mean levels were decreased in PMDD subjects during the luteal, compared with the follicular, menstrual cycle phase. In normal control subjects, melatonin rhythms did not change significantly with the menstrual cycle.

**Summary**

Studies that sampled plasma or serum melatonin more frequently (at 30-min intervals) suggest melatonin circadian rhythms are relatively stable and resistant to hormonal influences during the menstrual cycle in normal control subjects. In contrast, women with well-defined depressive disorders during the menstrual cycle have decreased melatonin amplitude measures associated with changes in phase markers in the symptomatic luteal phase, suggesting a decrease in the output of the circadian pacemaker that impairs the ability to regulate biological rhythms in depressed patients.

**Temperature rhythms**

Lee\textsuperscript{19} found a decrease of the temperature amplitude and an increase in the mesor in 17 healthy women during the luteal compared with the follicular menstrual cycle phase. The women’s acrophase was about 2 h earlier than published normative values in men. Additionally, Shibui et al.\textsuperscript{15} found core body temperature ($T_c$) amplitude was decreased significantly in the luteal compared with the follicular menstrual cycle phase in eight healthy women. The authors concluded that the increase of slow-wave daytime sleep during the luteal phase, associated with daytime sleepiness and positively correlated with daily mean $T_c$, was due to changes in thermoregulation in the luteal phase.

Severino et al.\textsuperscript{20} studied six women who either complained of premenstrual symptoms or met DSM-III-R\textsuperscript{21} criteria for late luteal phase dysphoric disorder (LLPDD). Symptomatic women had higher nocturnal $T_c$ than asymptomatic women across the menstrual cycle. The small sample size and mixed diagnoses limits meaningful interpretation of these findings. Parry et al.\textsuperscript{10} found a trend for earlier temperature minima, a marker for circadian phase position, in eight patients with premenstrual depression, compared with eight normal control subjects. In a larger follow-up study of 23 women with PMDD and 18 normal control subjects, Parry et al.\textsuperscript{22} found that 24-h $T_c$ amplitude was significantly decreased in the luteal compared with the follicular menstrual cycle phase.

**Summary**

Although most studies of temperature circadian rhythms during the menstrual cycle are hampered by small sample sizes and are not controlled for the masking effects of sleep on temperature, in toto they suggest a decrease of the temperature amplitude in the luteal phase, which like the findings from the melatonin studies, may indicate a decrease in the output of the circadian pacemaker. The effect may be to impair the ability to synchronize biological rhythms, making women more vulnerable to the development of depressive disorders at that time.

**Cortisol, TSH and prolactin rhythms**

**Cortisol**

Sampling hourly, Shibui et al.\textsuperscript{15} found the amplitude of cortisol rhythms was significantly lower in the luteal compared with the follicular menstrual cycle phase in eight healthy women undergoing ultrashort sleep-wake cycles. In a pilot study, Parry et al.\textsuperscript{23} observed increased plasma cortisol concentrations during the midcycle (late follicular) phase in eight women with prospectively documented PMS. In a larger study of 20 women with LLPDD\textsuperscript{21} and 11 normal control subjects, in whom cortisol
levels were measured every 30 min from 18:00 to 09:00 h during the midfollicular (MF) and late luteal (LL) phases, Parry et al. found that the cortisol peak was significantly delayed in the LL compared with the MF phase in normal control, but not in LLPDD, subjects. In a separate study of 15 women with PMDD and 15 normal control subjects, Parry et al. again observed altered timing, but not quantitative, measures of cortisol secretion in PMDD, in which the cortisol acrophase occurred about 1 h earlier in the LL versus MF phase in normal control, but not in PMDD, subjects.

Summary
Although few studies examine cortisol circadian rhythms in healthy women versus women with depressive disorders during the menstrual cycle, the available data suggest more group differences in the timing, rather than in the quantitative, measures of cortisol secretion.

TSH
In eight healthy women undergoing ultra-short sleep-wake cycle schedules, Shibui et al. found that the amplitude of the TSH rhythm sampled hourly was significantly decreased in the luteal compared with the follicular menstrual cycle phase. Additionally, Parry et al. found that TSH rhythms, measured every 30 min from 18:00 to 09:00 h during the MF and LL phases, occurred earlier in 23 PMDD compared with 18 normal control subjects.

Summary
Based on limited data, similar to the findings with cortisol, women with PMDD, compared with healthy control women, tend to have more timing than quantitative disturbances of TSH secretion.

Prolactin
Measuring prolactin every 30 min, Parry et al. observed that prolactin peak and amplitude were higher, and acrophase earlier in LLPDD patients \((n=20)\) than in normal control subjects \((n=11)\). Further research in 23 PMDD and 18 normal control subjects also showed that PMDD patients had higher prolactin concentrations, consistent with previous findings.

Summary
In contrast to cortisol and TSH, prolactin amplitude measures tend to differentiate PMDD versus normal control women during the menstrual cycle, although the findings are based on only two studies.

Challenge studies on the effects of wake therapy on mood, sleep and biological rhythms

Effects on mood and sleep
Parry and Wehr\(^{27}\) demonstrated the efficacy of total wake therapy (TWT) and the benefit of partial late-night wake therapy (LWT; sleep from 20:00 to 02:00 h) over partial early-night wake therapy (EWT; sleep from 02:00 to 08:00 h) for women with prospectively documented premenstrual syndrome (PMS). Parry et al. observed similar findings in 23 women with PMDD and 18 normal controls randomized to EWT or LWT with a night of recovery sleep after each wake therapy intervention. In PMDD subjects, Hamilton depression rating scale (HDRS)\(^{29}\) and Beck depression inventory (BDI)\(^{30}\) scores were significantly lower after recovery sleep than at baseline, with HDRS depression retardation symptoms being the most responsive to wake therapy. On the day after ESD or LSD, scores tended to be lower but were not significantly different from baseline. Sleep quality measures improved during recovery nights in PMDD, but not in normal control subjects. Changes in REM sleep measures were associated with clinical improvement in responders to wake therapy. Of note, most studies indicating shortened REM latencies in depressive disorders are in men; depressed women are less likely to exhibit this characteristic.

Effects of wake therapy on biological rhythms

Melatonin and temperature. Wright and Badia\(^{32}\) studied 25 healthy young women undergoing 24 h of sleep deprivation, using a modified constant routine procedure. They observed no significant differences between luteal and follicular phases in melatonin levels, duration or phase, but core body temperatures were higher in the luteal than in the follicular phase. Parry et al. reported that \(T_c\) amplitude increased after recovery nights of sleep from EWT and LWT in 23 PMDD and 18 NC subjects.

Cortisol. In a study of 15 PMDD and 15 normal control subjects in whom cortisol was measured every 30 min from 18:00 to 09:00 h after EWT and LWT interventions in the luteal phase, Parry et al. found that during LWT (when subjects’ sleep was shifted earlier), the cortisol acrophase was almost 2 h earlier in PMDD subjects.

TSH. In 23 PMDD and 18 normal control subjects, Parry et al. studied the effects of EWT and LWT interventions in the luteal phase on TSH rhythms measured every 30 min from 18:00 to 09:00 h.
Compared with baseline, wake therapy increased TSH amplitude measures (mesor and peak). The TSH timing measures (acrophase and peak time) occurred earlier in PMDD versus normal control subjects and were delayed during EWT when sleep was delayed.

Prolactin. In the study by Parry et al., prolactin levels decreased with wake therapy compared with baseline. The timing of prolactin secretion shifted earlier with LWT and later with EWT.

Summary. Although differences in biological rhythms in PMDD versus normal control women may not be evident in baseline studies, investigations that challenge sleep and other biological rhythms by interventions with wake therapy, highlight these differences and can provide corrective alterations in the relationship of sleep to other biological rhythms such as cortisol, TSH or prolactin. To date, however, these alterations have not correlated with therapeutic benefit.

Pregnancy

The hormonal changes of pregnancy, including estradiol, estriol, prolactin and cortisol, are illustrated in Fig. 2.

Sleep studies in healthy women during pregnancy

In early studies without well-defined sleep architecture, Branchey and Petre-Quadens recorded PSG in 17 pregnant women (10–40 weeks gestation) and found that isolated eye-movements and a prevalence of episodes of abnormal paradoxical sleep were maintained throughout the latter half of pregnancy. Paradoxical sleep increased gradually during pregnancy, peaking at 33-36 weeks and decreasing 3-4 weeks before delivery. In a subjective survey without objective sleep recordings of 100 women who were 38 or more weeks pregnant, Schweiger found that 68 women reported most sleep changes occurred in the third trimester, of sufficient severity in 12 women to take sleeping pills. PSG studies are relatively few, and their findings are inconsistent, but they generally suggest that stage 4 sleep decreases before delivery. In contrast, Driver et al. recorded PSG longitudinally, every 2 months from 8 to 16 weeks of gestation to 1 month postpartum, and found no reduction in stage 4 sleep with pregnancy. In fact, slow wave sleep (stages 3 and 4) was significantly higher at 27-39 weeks than at 8-16 weeks; REM sleep was unchanged. These findings are consistent with a restorative theory of sleep and the effects of changing levels of cortisol and progesterone on sleep. Hertz et al., in a cross-sectional study of 12 third-trimester women, found that wake after sleep onset and stage 1 sleep increased significantly, and sleep efficiency and REM sleep (%) decreased compared with age-matched, non-pregnant control women. Brunner et al. reported a progressive reduction of power density during the course of pregnancy, hypothesized to be associated with hormonal changes, although no hormonal measures were obtained. In a questionnaire study, Fujino et al. found bedtime occurred gradually later as gestation progressed, particularly in women ≤ 24 years of age. Schorr et al., in a longitudinal study of four pregnant women for one night (no adaptation night) during each trimester during pregnancy, and of four non-pregnant women, found reduced sleep stages 3 and 4 in pregnant women. Lee et al., using home recordings by ambulatory monitoring in 33 women at 11-12, 23-24 and 35-36 weeks of gestation, found an increase in total sleep time by 11-12 weeks gestation, but less deep sleep and more awakenings. In-home ambulatory monitoring, however, may differ from inpatient PSG recordings. Wolfson et al. studied 38 primiparous
women during the last trimester of pregnancy and at 2–4 weeks, 12-16 weeks and 12-15 months postpartum using a sleep-wake diary and a self-rating depression scale. Mothers who developed depressive symptoms at 2–4 weeks postpartum reported more total sleep time, later rise times and more time napping at the end of pregnancy. No objective measures of sleep, mood or reproductive hormones were obtained.

Sleep studies in women with mood disorders during pregnancy

Karacan et al.45 studied three women during early, and 10 during late, pregnancy. Based on their findings, they suggested that increases in sleep latency, number of awakenings and amount of stage 0 sleep, together with decreases in stages 1, 4 and REM sleep, particularly during late pregnancy, provided a basis for developing postpartum emotional disturbances. Diagnostic criteria for depression were not used, however. Frank et al.46 studied women with a recurrent major depressive episode (MDE), whose onset of illness began during pregnancy or within 6 months postpartum. Compared with 28 women without pregnancy-related episodes, the 24 women with postpartum episodes had significantly longer REM time and more REM activity, suggesting a greater biological vulnerability to depression. Coble et al.47 examined PSG sleep in childbearing women with (n=14) and without (n=20) a history of mood disorder (minor and major depression, hypomania). In women with a history of mood disorder, childbearing was associated with greater changes in total sleep time, and with REM reduction evidenced earlier in the childbearing course, and persisting throughout the 8 month postpartum. The findings support the association between sleep abnormalities and a vulnerability to mood disorders. As Roberts et al.48 suggest, sleep disturbances diagnostic for a MDE are strongly associated with the risk of future depression.

Summary

Sleep studies of normal control women during pregnancy are inconsistent. Although some of the earlier studies with relatively small sample sizes suggest a decrease in slow wave sleep, the later, more rigorous studies, which include adaptation nights, larger sample sizes, objective measures of sleep and well-defined diagnostic groups, do not support these findings. Studies of patients with well-defined mood disorders tend to be more consistent in that vulnerability markers, particularly REM sleep measures (density, minutes, percent), are more prevalent in depressed patients with a history of a mood disorder (see Table 2).

Biological rhythms in pregnant women

Biological rhythms in healthy women during pregnancy

Melatonin. Pang et al.49 examined plasma levels of immunoreactive melatonin, estradiol, progesterone, FSH and β-human chorionic gonadotropin (βhCG) during pregnancy and shortly after parturition in 105 Chinese women. In pregnant women, there were significant negative correlations between melatonin and estradiol, melatonin and progesterone, βhCG and progesterone and βhCG and estradiol; and positive correlations between melatonin and FSH, and progesterone and estradiol. The findings suggest that gonadal steroids inhibit, and FSH potentiates, circulating melatonin levels in gravid women. Circulating melatonin in the mother may affect in utero development and be the major source of blood melatonin in the fetus before parturition. Kivela50 studied 12 women in early, and 11 women in late, pregnancy and found that serum melatonin levels, sampled every 4 h during the third trimester of pregnancy, were significantly higher than those during the first and the second trimester and those of non-pregnant control women. Serum melatonin concentration at 11:00 h was positively correlated with gestation week. Amplitude and duration of the nocturnal melatonin rise were higher during late pregnancy, but there was no clear phase-shift. Suzuki et al.51 examined pregnant women and compared melatonin secretion rhythms sampled hourly from 18:00 to 08:00 h in six good sleepers and six poor sleepers. Melatonin levels, as determined by polynomial curve-fitting techniques, differed significantly between the poor sleeper group (lower values) and the good sleeper group (higher values). Non-significant trends were found for increased amplitude in the melatonin rhythm in poor sleepers. The differences may reflect changes in the circadian pacemaker system of poor sleepers, with increases in melatonin release being a response to counteract poor sleep. Nakamura et al.,52 sampling at 14:00 and 02:00 h in 79 pregnant women (timing during pregnancy not specified), reported increases in maternal serum melatonin until the end of pregnancy, which decreased to non-pregnant levels by the second postpartum day.

Summary. Some of the inconsistencies in the studies of melatonin circadian rhythms during
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<tr>
<th>Authors</th>
<th>N</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>NC Branchey and Petre-Quadens</td>
<td>17</td>
<td>PSG PG W 10-40 wks</td>
<td>PS, REM peak 33-36 wks, then decline</td>
<td>Not well-defined sleep architecture, no RH</td>
</tr>
<tr>
<td>(1968)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schweiger</td>
<td>100</td>
<td>Subjective sleep reports</td>
<td>Sleep disturbances occur in 3rd trimester</td>
<td>No objective sleep measures, no RH</td>
</tr>
<tr>
<td>(1972)</td>
<td></td>
<td></td>
<td>Stage 4 sleep before delivery</td>
<td>Only 3 women studied across trimesters, no RH</td>
</tr>
<tr>
<td>Karacan et al.</td>
<td>13</td>
<td>PSG late pregnancy and postpartum W 22-30 yrs</td>
<td>SWS 27-39 wks. No change in REM</td>
<td>Only 5 primiparous women, only 1st 6 h. of sleep analyzed, no RH</td>
</tr>
<tr>
<td>(1967)</td>
<td></td>
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<tr>
<td>Driver et al.</td>
<td>5</td>
<td>PSG every 2 mo. during pregnancy starting 8-16 wks. gestation; 1 mo. postpartum</td>
<td></td>
<td></td>
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<tr>
<td>(1992)</td>
<td></td>
<td></td>
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<tr>
<td>Hertz et al.</td>
<td>12</td>
<td>PSG in 3rd trimester W versus non-PG controls</td>
<td>↑WASO, Stage 1; ↓REM sleep, SE in PG W Progressive reduction of power density during pregnancy</td>
<td>Not longitudinal study, no RH</td>
</tr>
<tr>
<td>(1992)</td>
<td></td>
<td>Spectral analysis ×2 nights each trimester</td>
<td></td>
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<tr>
<td>Brunner et al.</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>(1994)</td>
<td></td>
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<tr>
<td>Fujino et al.</td>
<td>1968</td>
<td>Questionnaire study to PG W and non-PG W, M</td>
<td>Bedtime later in later gestational wks in W &lt; 24 years</td>
<td>No objective measures, no RH</td>
</tr>
<tr>
<td>(1995)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Schorr et al.</td>
<td>8</td>
<td>4 PG and 4 non-PG inpatients PSG ×1 each trimester</td>
<td>↑TST, ↓deep sleep, ↑awakening during sleep by 11-12 wks of conception</td>
<td>No adaptation nights, no RH</td>
</tr>
<tr>
<td>(1998)</td>
<td></td>
<td>Home recordings 11-12, 23-24, 35-36 wks. PG</td>
<td>↑TST, later rise time, ↑naps 3rd trimester in W with ↑depressive SXS</td>
<td>In-home PSG results may differ from inpatient PSG</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(2000)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wolfson et al.</td>
<td>38</td>
<td>Sleep-wake diaries and depression self-rating 3rd trimester; 2-4 wks, 12-6 wks, 12-15 mo PP</td>
<td></td>
<td>No objective measures of sleep, mood or RH</td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DP Karacan et al.</td>
<td>13</td>
<td>PSG early pregnancy 4-6 wks, 1 night every 2 wks; 10 W late pregnancy ×3 nights-10 days before delivery</td>
<td>↑SL, WASO, ↓Stages 1 and 4, REM in late pregnancy</td>
<td>Small N each time period, no diagnostic criteria DP, no RH</td>
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<td>(1969)</td>
<td></td>
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<tr>
<td>Frank et al.</td>
<td>24 DP 28 NC</td>
<td>PSG in W 12 wks PG-8 mo. PP. Home recordings</td>
<td>DP (PP) ↑REME time and activity DP ↓TST, REM (2-3 mo. to 8 mo. PP); ↓RL 3rd trimester</td>
<td>Findings in W PP, not pregnancy MDE, no RH</td>
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<tr>
<td>(1987)</td>
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<tr>
<td>Coble (1994)</td>
<td>14 20 NC</td>
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Sleep, mood and women's reproductive cycle
pregnancy may be attributed to different sampling frequencies, assay and analytic methods, and variations in the influence of sleep patterns and gonadal steroid levels. In toto, amplitude measures of melatonin tend to increase in the later stages of pregnancy and are more marked than phase changes.

Cortisol, TSH, prolactin

**Cortisol.** Eriksson et al. sampled cortisol at 30-min intervals (circadian time epoch not specified) in two women in early pregnancy (11–17 weeks), four in late pregnancy (34–38 weeks) and in two non-pregnant control women. They found increased cortisol concentrations in pregnant women with maintenance of the diurnal rhythm, in that the nadir levels occurred around midnight and there were marked elevations during the early morning hours. Suzuki et al. found a non-significant trend towards decreased amplitude in the cortisol rhythm in pregnancy, which, in poor sleepers, was due to a suppression of the early morning rise (05:00-08:00 h).

**TSH.** Eriksson et al. found that diurnal variation in TSH was maintained during pregnancy, with maximal values around midnight as in non-pregnant women.

**Prolactin.** Boyar et al. found that in three pregnant women during pregnancy, episodic prolactin secretion, measured at 20-min intervals for 24 h at 12, 20, and 32 weeks gestation, became augmented during nocturnal sleep, with increased mean prolactin levels achieved by increased secretion per secretory episode. Eriksson et al. also reported episodic secretion of prolactin during pregnancy. In the study by Suzuki et al., prolactin levels were high and showed no rhythmicity in both groups of pregnant good sleepers and poor sleepers.

**Biological rhythms in women with mood disorders during pregnancy**

Parry et al. measured plasma melatonin every 30 min from 18:00 to 11:00 h in dim (<30 lux)/dark conditions in eight women with a MDE during pregnancy and four normal control subjects matched for age (within 5 years) and weeks pregnant (within 4 weeks). Depressed patients had significantly earlier mean melatonin offset time, and lower peak and area under the curve than normal control subjects. Mean cortisol levels from 18:00 to 01:30 h were significantly lower in depressed patients than in normal controls. The ratio of cortisol to melatonin from 04:00 to 11:00 h, however, was higher in depressed patients than in normal control subjects. Higher mean prolactin levels were found in depressed patients than normal control subjects when weeks pregnant and body mass index (BMI) were applied as covariates in the analyses. There was a non-significant trend toward lower mean TSH levels in depressed compared with normal control subjects.

**Effects of wake therapy on mood during pregnancy**

In case reports, Parry et al. observed that EWT (sleep 03:00-07:00 h) or LWT (sleep 21:00-01:00 h) had beneficial effects on mood in women with a MDE during pregnancy.

**Summary**

Although studies that examine the circadian rhythms of cortisol, TSH and prolactin during pregnancy are few in number with small sample sizes, and interpretations are limited by the different methodologies employed, most studies suggest diurnal rhythms are maintained during pregnancy, with more changes observed in amplitude than in phase. Based on one small study, pregnant women with a MDE had lower mean melatonin amplitude (peak and area under the curve), and lower mean evening cortisol levels than healthy women. Critically timed wake therapy may benefit some depressed women during pregnancy, but the effect on neuroendocrine rhythms in relation to sleep is unknown.

**Postpartum**

Hormonal changes during the postpartum period for estradiol, progesterone, FSH, LH and prolactin are illustrated in Fig. 3.

**Sleep studies in healthy women postpartum**

Using subjective ratings, Swain et al. reported that 30 primiparous women had more evening awakenings, more time awake after retiring and more naps than 28 non-postpartum mothers, but sleep time was similar. Although postpartum women reported more dysphoric mood than controls in the first postpartum week, controlling for time awake at night eliminated the significant effect for dysphoric mood. Waters and Lee compared 12 primigravidae with 19 multigravidae. Primigravidae experienced significantly more
fatigue and disturbed sleep, third trimester sleep efficiency falling from 90 to 77% postpartum, while multigravidae had only a minor reduction in sleep efficiency. In a study of seven Japanese women, Horiuchi et al.\textsuperscript{59} reported that by postpartum (subjective) sleep logs, wake time at night gradually decreased from 5th to 12th week. Hormonal measures were not specified in these studies.

From PSG assessments, most studies suggest REM sleep decreases after delivery.\textsuperscript{35-37} Hertz et al.\textsuperscript{39} noted only a slight increase in REM sleep in seven women postpartum, compared with the prepartum period. By 3-5 months postpartum, they observed increased sleep efficiency and a significant reduction in wake after sleep onset. Lee et al.\textsuperscript{43} studied 31 women and reported that compared with the third trimester of pregnancy, REM latency was significantly shorter at 1 month postpartum, when mood state was most negative (diagnoses were not made by psychiatric interview). In a cross-sectional study, Nishihara et al.\textsuperscript{60} compared 12 non-pregnant Japanese women with 10 primipara at home from 9 to 12 weeks postpartum, using a Medilog recorder. Postpartum women had more interrupted sleep, lower sleep efficiency, decreased total sleep time, decreased stage 2 (%) and increased stage 4 (%) sleep. Blyton et al.\textsuperscript{61} found that postpartum women (n=12) who breast-fed babies (from 4 to 30 weeks) had increased slow wave sleep, and a compensatory reduction in light NREM sleep compared with women who bottle fed infants (n=7), or age-matched control subjects (n=12) studied during the follicular menstrual cycle phase. By actigraphic studies in 10 women measured from the fifth prepartum to the 15th postpartum week, Kang et al.\textsuperscript{62} found total sleep time and sleep efficiency deteriorated significantly, compared with late pregnancy, for 12 weeks after delivery. A lengthened period of wake after sleep onset persisted for 10 weeks postpartum. Studying arousal to auditory stimulation in six women, Poitras et al.\textsuperscript{63} reported that compared with pregnancy (9-30 days before delivery), there was a significant lowering of awakening threshold postpartum, 22-70 days after delivery, during stage 2, REM and slow-wave sleep.

**Figure 3** Serum concentrations of prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (hCG), estradiol (E\textsubscript{2}) and progesterone (PROG) in lactating and non-lactating women in the puerperium. The M bars refer to non-lactating women’s menstrual periods (redrawn with permission from Liu J, Rebar RW, Yen SS. Neuroendocrine control of the postpartum period. \textit{Clin Perinatol}. 1983; 10(3):723-736).

**Sleep studies in women with mood disorders postpartum**

Only published abstracts were available

**Summary**

Marked variation in the methodologies employed makes it difficult to compare postpartum sleep findings across studies and cultures. Besides small sample sizes, studies lack longitudinal design and documentation of postpartum week or hormonal status, and are limited by the fact that sleep may be affected by parity, lactation and depressed mood. Generally, the findings suggest that postpartum
sleep is disrupted and does not return to baseline levels until at least 12 weeks postpartum (at which time the infant’s sleep and melatonin rhythms tend to establish diurnal patterns) (see Table 3).

**Biological rhythms postpartum**

**Biological rhythms in healthy women postpartum**

**Prolactin.** In a rigorous endocrine study with frequent blood sampling at 20-min intervals for 12–24 h, Liu and Park measured prolactin concentrations weekly on postpartum days 10–26 in eight non-lactating postpartum women. While serum prolactin levels remained elevated during this time, the diurnal pattern of secretion persisted, with concentrations declining across postpartum weeks. Asher et al. examined plasma prolactin levels between 08:00 and 09:00 h just prior to delivery and 3 days after delivery in 25 healthy postpartum women. The rise in plasma prolactin levels postpartum was negatively correlated with scores on the Hamilton anxiety scale, suggesting that the elevated plasma prolactin during lactation reduced anxiety symptoms in lactating women.

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>NC</td>
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<tr>
<td>Swain et al. (1997)</td>
<td>30 PP 28 NPP</td>
<td>Subjective ratings pg W</td>
<td>PP W &gt; p.m. awakenings, ↑ WASO, ↑ naps than controls pg &gt; fatigue and disturbed sleep than MG</td>
<td>No objective measures of sleep, no RH</td>
</tr>
<tr>
<td>Waters and Lee (1996)</td>
<td>12 pg 19 MG</td>
<td>EEG, EOG by medilog ambulatory monitoring</td>
<td>Sleep logs 5-12 wks. PP</td>
<td>No hormonal measures</td>
</tr>
<tr>
<td>Horiuchi and Nishihara (1999)</td>
<td>7 PP</td>
<td>Sleep logs 5-12 wks. PP</td>
<td>↓ WASO from 5 to 12th wk PP</td>
<td>No objective sleep measures, no RH</td>
</tr>
<tr>
<td>Hertz et al. (1992)</td>
<td>7 PP 10 NPP</td>
<td>PSG 3-5 mo. PP</td>
<td>↓ WASO, ↑ SE, slight ↑ in REM</td>
<td>Measures made later in PP course; variable F, L phases, no RH</td>
</tr>
<tr>
<td>Lee et al. (2000)</td>
<td>31 PP</td>
<td>PSG at home × 2 nights, 1 mo. PP</td>
<td>↓ RL at 1 mo. PP in W with negative mood PP ↑ interrupted sleep, ↓ SE, ↓ TST, ↓ Stage 2 (%), ↑ Stage 4 (%)</td>
<td>No diagnostic criteria for negative mood Not longitudinal study, no RH</td>
</tr>
<tr>
<td>Nishihara et al. (2001)</td>
<td>10 PP 12 NPP</td>
<td>Home Medilog recording 9-12 wks. PP × 1 night</td>
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<tr>
<td>Blyton et al. (2002)</td>
<td>12 BF 12 BTL 12 CTRL</td>
<td>PSG 4-30 wks. PP; CTRL W F phase</td>
<td>↓ SWS and ↓ light NREM sleep in BF W</td>
<td>Wide variations in PP wks (4-30), no RH</td>
</tr>
<tr>
<td>Kang et al. (2002)</td>
<td>10 PP</td>
<td>Actigraphy 5th prepartum-15th PP wk</td>
<td>↓ TST, SE; ↑ WASO until 12th PP wk</td>
<td>Sleep by actigraphic recordings worse than by sleep logs, no RH</td>
</tr>
<tr>
<td>Poitras et al. (1973)</td>
<td>6 pg and PP</td>
<td>PSG 9-30 days before delivery and 22-70 days after delivery with auditory stimuli</td>
<td>↓ Awakening threshold PP in Stage 2, REM, SWS</td>
<td>Wide variation in study days, no RH</td>
</tr>
</tbody>
</table>

BF, breast-feeding; BTL, bottle-feeding; CTRL, controls; DP, depressed patients; EGG, electroencephalogram; EOG, electrooculogram; F, follicular; L, luteal; MG, multigravida; MO, months; NC, normal controls; NPP, non-postpartum; NREM, non-REM sleep; pg, primigravida; P.M., post meridian; PP, postpartum; PSG, polysomnography; REM, rapid eye movement; RH, reproductive hormones; RL, REM latency; SE, sleep efficiency; SWS, slow wave sleep; TST, total sleep time; W, women; WASO, wake after sleep onset; WKS, weeks.
Biological rhythms in women with mood disorders postpartum

**Melatonin.** Parry et al. measured plasma melatonin every 30 min from 18:00 to 11:00 h in dim (< 30 lux)/dark light in 11 women with a MDE postpartum and five postpartum normal control women matched for age and postpartum month. Depressed patients had a trend towards a higher mean melatonin peak and area under the curve compared with normal control subjects. Timing measures (onset, offset, duration) were not significantly different between groups.

**Cortisol, TSH, prolactin**

**Cortisol.** Harris et al. assayed saliva for cortisol and progesterone, twice daily from 2 weeks before delivery to day 35 postpartum in 120 primiparous women. Seven women developed major depression postpartum. Lower levels of evening cortisol, but not progesterone, in the immediate peripartum period were associated with postnatal depression.

**TSH.** Parry et al. sampled TSH overnight at 30-min intervals and found no statistically significant differences in depressed versus normal control women postpartum.

**Prolactin.** Harris et al. observed that in 147 postpartum mothers, 15% of whom were depressed, plasma prolactin levels were inappropriately low in depressed women who breast-fed. Abou-Saleh et al. found significantly lower plasma prolactin levels in a single morning sample in women with postpartum depression. In a study of 11 women with a MDE postpartum and five normal control women matched for age and postpartum month, in which serum samples for prolactin were obtained every 30 min from 18:00 to 11:00 h, Parry et al. found that both breast-feeding and non-breast-feeding depressed patients had significantly increased mean prolactin amplitude compared with normal control women.

**Summary**

The studies are limited by small sample sizes and lack of frequent hormonal sampling to assess circadian rhythmicity. Based on the limited available data, melatonin and prolactin tend to be increased in women with a MDE postpartum compared with healthy women. In contrast, in healthy postpartum lactating women, higher prolactin levels were associated with decreased anxiety. Cortisol levels tended to be lower rather than higher in postnatal depression as in atypical depression. In the early postpartum period, prolactin, but not cortisol, secretion patterns can be affected by the type of delivery (Caesarean versus vaginal route). Prolactin also may be affected by lactation and amenorrhea. No significant differences were found between depressed and healthy postpartum women in TSH. The relationship of these neuroendocrine hormones to sleep in depressed versus healthy postpartum women has not been reported.

**Effects of wake therapy on mood, sleep and biological rhythms in postpartum women**

**Women with mood disorders**

Strouse et al. found that partial wake therapy elicited mania or hypomania in three hospitalized women with postpartum psychosis without a prior history of psychotic disorder, suggesting that psychosis in these patients represented a variant of bipolar mood disorder. Parry et al. reported beneficial effects, particularly of LWT, in women with a MDE postpartum: after recovery sleep from LWT (sleep 21:00–01:00 h), Hamilton depression rating scores were reduced significantly after LWT ($p < .012$), but not after EWT (sleep 03:00–07:00 h) or dim red light (during habitual sleep time). After the LWT intervention, seven of seven depressed women met criteria for response (greater than 40% decrease in symptoms).

**Summary**

The findings suggest a potential for marked antidepressant effects of wake therapy in postpartum women with mood disorders. The effects on biological rhythms (melatonin, cortisol, TSH and prolactin) remain unknown.

**Conclusions**

Studies of sleep in relation to other biological rhythms during the menstrual cycle, pregnancy and the postpartum period in women with depressive disorders and healthy control subjects generally are limited by lack of well-defined diagnostic criteria in depressed patients, control subjects matched for age and reproductive status, hormonal measures to define phase of the reproductive epoch during the menstrual cycle, pregnancy, or postpartum, objective measures to record sleep or mood, longitudinal design or circadian sampling. Based on more
methodologically-sound studies that use objective measures in groups defined by diagnostic criteria, sleep tends to be more disturbed, with impairment in measures of sleep quality, premenstrually, during the last trimester of pregnancy and during the first 12 weeks postpartum, especially in predisposed women with a history of a mood disorder. In comparison with matched healthy women, in women meeting diagnostic criteria for a depressive disorder, melatonin circadian rhythms were decreased in PMDD and in women with a MDE during pregnancy, whereas they were increased in women with a postpartum MDE. Women with PMDD, postpartum or pregnancy-related depressive disorders had increased levels of prolactin circadian rhythms compared with matched normal control subjects (when weeks pregnant and BMI were used as covariates in the analyses). Since age, weeks pregnant or postpartum, BMI and breast-feeding status may alter neuroendocrine function substantially, controlling for these variables either statistically or methodologically is essential to provide a basis for rigorous interpretations of results. In women with pregnancy-related MDE, cortisol circadian rhythms were lower, rather than higher, compared with healthy controls, a finding reported previously in post-traumatic stress disorder. Challenges with wake therapy improved mood in a majority of women with PMDD or a postpartum MDE, although the effect on biological rhythms was not correlated with clinical response. More work is needed to test the hypothesis that disturbances in the phase or amplitude of circadian rhythms in relation to sleep characterize women with depressive disorders related to the reproductive cycle.

Research agenda

1. Studies in sleep and biological rhythms should specify mood disorders using standard diagnostic criteria to differentiate patients with depressive disorders from normal controls.
2. Studies of sleep and biological rhythms in women should carefully distinguish reproductive state, i.e. phase of the menstrual cycle, and week pregnant or postpartum, by reproductive hormone levels.
3. Studies of biological rhythms should measure diurnal variation and its relationship to sleep.

Acknowledgements

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References

10. Parry BL, Mendelson WB, Duncan WC, Sack DA, Wehr TA. Longitudinal sleep EEG, temperature, and activity

Practice points

1. Sleep tends to be disrupted premenstrually with more awake time after sleep onset. In normal subjects, biological rhythms are relatively stable across the menstrual cycle.
2. Sleep, particularly in the later stages of pregnancy, may become disrupted.
3. Sleep patterns generally do not return to baseline until about 3 months postpartum, when melatonin and the sleep/wake cycle establish diurnal patterns.

* The most important references are denoted by an asterisk.


36. Roffwarg HP, Frankel BL, Pessah M. The nocturnal sleep pattern in pregnancy. In: *Annual meeting of the association for the psychophysiological study of sleep; March 1968*.


