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ORIGINAL ARTICLE

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Oral contraceptives alter sleep and raise body temperature in young women

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Abstract Female reproductive steroids, oestrogen and progesterone, not only affect reproductive function, but also thermoregulation and sleep. Chronic administration of synthetic steroids, as occurs in women taking oral contraceptives, may affect these regulatory systems differently from endogenous oestrogen and progesterone. We therefore investigated body temperature and sleep in ten young women taking oral contraceptives, in the active and placebo phases of the contraceptive pack, and compared them to a group of nine women with ovulatory cycles, in the mid-follicular and mid-luteal phases. Body temperature was raised throughout 24 h in the women taking oral contraceptives in the active phase, and in the naturally cycling women in the luteal phase, compared to the follicular phase. The women taking oral contraceptives in the placebo phase, however, continued to have raised body temperatures, similar to those in the active phase, indicating a prolonged action of synthetic reproductive steroids on body temperature. Sleep also was influenced by the endogenous and synthetic reproductive steroids, but independently of body temperature. The women taking oral contraceptives had more stage-2 non-rapid eye movement sleep in the active phase, both compared to their placebo phase and the naturally cycling women. The naturally cycling women, however, had more slow wave sleep in the luteal phase compared to the contraceptive group of women. Exogenous reproductive steroids therefore influence body temperature and sleep differently from endogenous progesterone and oestrogen.

Keywords Menstrual cycle · Oestrogen · Progesterone · Slow wave sleep

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Introduction

The steroid hormones oestrogen and progesterone not only mediate reproductive function, but also influence other regulatory processes, such as thermoregulation, in young women. Daily average body temperature increases by approximately 0.4°C in the luteal phase of the ovulatory cycle, associated with an increase in progesterone, compared to the pre-ovulatory follicular phase [8,14]. In contrast, body temperature decreases just before ovulation, associated with the surge in oestrogen, compared to the early follicular phase [36]. Progesterone and oestrogen also may influence the circadian rhythm of body temperature. Some studies have found that women have blunted circadian amplitudes [8, 24,31] and a delayed circadian phase [8] of the body temperature rhythm in the luteal phase compared to the follicular phase, whereas others have found no circadian differences between menstrual phases [4,38]. The mechanism of reproductive steroid influence on body temperature remains to be clarified in humans, but the discovery of progesterone and oestrogen receptors in the hypothalamus [2], where body temperature is controlled, and the responsiveness of temperature-sensitive neurons to oestrogen [35] and progesterone [30] implies that they may act centrally to change body temperature regulation, either directly [35] or indirectly through mediators, such as cytokines [9].

Synthetic steroids, contained in oral contraceptives, may influence thermoregulation in a manner similar to that of endogenous steroids. Indeed, women taking contraceptives containing oestrogen and progestin, when they are awake, have elevated rectal temperatures and sweating thresholds, similar to those in naturally cycling

women in the luteal phase, at rest, during exercise and after passive heating [10,34]. Women taking oral contraceptives also have similar body temperature profiles over 24 h, with temperature nadirs occurring at a similar time compared to ovulating women in the luteal phase [4, 24,38]. Exogenous steroids, however, are more potent than endogenous hormones [34], and may remain active in the brain for a longer period. Whereas body temperature rapidly falls at the end of the luteal phase, associated with a decline in progesterone and oestrogen in naturally cycling women [11], women taking oral contraceptives may [24] or may not [10,34] continue to have elevated body temperatures during the placebo phase of the contraceptive pack, even though synthetic hormones are no longer being administered. The effects on body temperature of the chronic administration and withdrawal of synthetic steroids therefore are not yet firmly established.

Apart from their effects on body temperature, reproductive steroids influence sleep. Although there have been numerous studies investigating sleep during the natural menstrual cycle, the findings once again are inconsistent (see [13] for review). In the luteal phase, rapid eye movement (REM) sleep has been reported to be either reduced [3,14] or unchanged [4], and stage-2 non-REM sleep has been reported to increase in association with increased activity in the spindle frequency range (12–15 Hz) [14,22], or remain unchanged [3,28]. Changes that occur in sleep during the menstrual cycle are thought to be associated with changes in progesterone [14], but the variability and the confounding interactions that occur between hormonal systems in the menstrual cycle make it difficult to attribute any variation in sleep to one hormone. To identify the effects on sleep of progesterone, researchers therefore have investigated sleep in young men or in ovariectomized rats after administering synthetic progesterone. An acute dose of progesterone increases non-REM sleep both in young men [18] and in rats [26], and administration to rats of allopregnanolone, a progesterone metabolite, increases slow wave sleep (SWS) [37]. Chronic administration of synthetic steroids, as in young women who are taking oral contraceptives, may influence sleep differently from an acute dose. Ho [21] found a decrease in SWS in three women taking oral contraceptives compared to that in three naturally cycling women, a finding which we confirmed in a recent study of eight women [4]. Lee et al. [28], however, found no differences in sleep except for a reduction in REM sleep-onset latency (ROL) in three women taking oral contraceptives compared to naturally cycling women. Since the effects of the natural menstrual cycle on sleep are so variable, it is more appropriate to compare sleep in the same group of women when they are taking synthetic hormones compared to when they are not. Women who take monophasic oral contraceptives are a suitable group to study the influence on sleep of the chronic administration and withdrawal of synthetic steroids, because they take a combined oestrogen and progestin pill daily for 3 weeks, and a placebo pill for the remaining week, in every month.

Sleep, in women taking oral contraceptives, may be influenced not only by the exogenous hormones directly, but also by the associated body temperature changes. Some researchers consider body temperature and sleep to be closely coupled; sleep onset evokes a decrease of core body temperature [5] and conversely a rapid decline in core body temperature associated with peripheral heat loss increases the likelihood of sleep initiation [25]. However, we did not find a strong relationship between body temperature and sleep in young women with ovulatory menstrual cycles, women taking oral contraceptives in the active phase, or in young men [4]. In that study, though, we did not measure body temperature and sleep in the placebo phase of the women taking oral contraceptives.

The association between endogenous or exogenous reproductive steroids, body temperature and sleep needs further exploration. We therefore measured sleep and body temperature in women taking synthetic progestins and oestrogens, and placebo tablets, in the oral contraceptive pack, and compared them to naturally cycling women in the follicular and luteal phases of their menstrual cycles. We used newly developed thermometric data loggers to measure body temperature in freely behaving subjects over 24 h.

Subjects and methods

Subjects

Eleven healthy young women who were taking oral contraceptives and 12 naturally cycling women without any menstrual-associated complaints were recruited from a university student population and consented to participate in our study. Ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (Clearance no. M00/2/4), which adheres to the principles of the Declaration of Helsinki. All the subjects completed questionnaires and were interviewed to ensure that they had regular sleep-wake schedules, were non-smokers, and showed no indication of sleep or medical disorders. The 30-item version of the General Health Questionnaire, which correlates well with psychiatric interview [20], was used to screen the volunteers for psychological disorders; all the volunteers scored less than 12 out of 30, indicating normal psychological status. The women were asked specifically about any mood changes that occurred during their menstrual cycles and also completed a screening questionnaire for dysmenorrhoea [1]. None reported evidence of premenstrual syndrome [29] or dysmenorrhoea [1].

Women selected for inclusion in the group taking oral contraceptives had been taking monophasic oral contraceptives (21 active pills containing a fixed dosage of oestradiol and synthetic progestin; 7 placebo pills) voluntarily for between 4 months and 5 years before the study. Five women were taking hormonal preparations containing 0.03 mg ethinyl-oestradiol and 0.15 mg of either desogestrel (Donmed Pharma) or levonorgestrel (Akromed). Three women were taking 0.03 mg ethinyl-oestradiol and 0.075 mg gestodene (Schering). One woman was taking 0.05 mg ethinyl-oestradiol with 0.25 mg levonorgestrel (Akromed), and one woman had 0.035 mg ethinyl-oestradiol with 2.0 mg cyproterone acetate (Schering). Six of the women habitually took the pill in the evening and the remaining five women took the pill in the morning. The naturally cycling women had not taken any hormonal contraceptives for at least 6 months before our study.

Experimental procedure

For 1 month after entering the study, the naturally cycling women completed a calendar of premenstrual experiences [29], which confirmed that none suffered from premenstrual syndrome. They also recorded the dates of their menses. They measured their oral temperature every morning before getting out of bed, using a digital thermometer (Soar M.E., Nagoya, Japan), and used a commercially available self-test kit which detects the presence of luteinizing hormone (LH) in urine (ClearPlan One Step, Unipath, Bedford, UK) to confirm ovulation. All 12 women had regular, ovulatory menstrual cycles, as assessed by a mid-cycle surge of LH and a post-ovulatory increase in oral temperature.

Recordings were made over a 6-month period during the summer and autumn months. All the subjects were requested to maintain their customary weekday bedtime schedules, even on the weekend, for at least 1 week before a scheduled study night. On study nights, the subjects followed an identical night-time protocol in which they maintained their habitual schedules but slept in the controlled environment of our laboratory. All the women spent at least three nights in the laboratory, one adaptation night and two recording nights. The women taking oral contraceptives came for one recording at least 3 days after they had started taking the active contraceptive pill (active phase), and for their other recording at least 3 days after they had taken the final active contraceptive pill (placebo phase). The naturally cycling women came once during the mid-follicular phase (7–10 days after the onset of menstrual flow) and once during the mid-luteal phase (either the fifth or sixth night after the LH surge). The adaptation night allowed the subjects to familiarize themselves with the new environment and recording equipment. All of the women had their adaptation night one or two nights before their first recording night. Seven of the women taking contraceptives had their first recording night in the active phase, and five of the naturally cycling women had their first recording night in the luteal phase. Eight of the women taking oral contraceptives had two recording nights in each phase, but only the second night was analysed. The remaining three women taking oral contraceptives and all of the naturally cycling women had only one recording night in each phase. On study days, the subjects were allowed to pursue their usual daytime activities, such as attending lectures, but they refrained from drinking caffeinated or alcoholic beverages, and did not participate in any strenuous exercise for 8 h before the start of the sleep recordings. We asked the subjects not to shower or bath in the evening of their recording nights, but we did not prohibit them from showering in the morning. We also did not regulate food intake or posture during the study. For the sleep recordings all the subjects wore light sleeping attire and slept under an eiderdown quilt, each in a separate bedroom, where the ambient temperature was maintained between 21 and 23°C. Lights-out and lights-on times were self-selected, based on the customary weekday bedtime schedules for each individual, and were kept the same for both recording nights. Lights were turned off between 22:00 and 24:00 hours and were turned on between 7 and 8 h later.

Data acquisition and analysis

Standard polysomnographic electroencephalographic, electro-oculographic and electromyographic recordings were made on a digital electroencephalograph (Medelec DG 20, Vickers Medical, Surrey, UK) at a virtual recording speed of 15 $mm \cdot s^{-1}$. Twenty-second epochs were scored according to modified standard criteria [33] by one scorer (FCB) blind to the identity of the subject or recording phase. Total time spent in bed refers to the time from lights-out to lights-on. Sleep efficiency was calculated as a percentage of total time spent asleep over the first 7 h after lights-out for each subject. Sleep-onset latency (SOL) was taken as the time from lights-out to the appearance of the first of at least three consecutive epochs (60 s) of stage-2 sleep. The time between sleep onset and the first indication of any REM sleep was the ROL. The latency to SWS was the time from sleep onset to the first of at least 60 s of stage-3 sleep.

Rectal temperatures were recorded every minute for at least 24 h, starting in the evening of the recording night, using indwelling rectal thermistors connected to miniature temperature data loggers (Stowaway XTI, Onset Computer Corporation, Pocasset, Mass., USA), custom-modified to have a narrow temperature range (34 to 46°C) and high resolution (0.04°C). The thermistors were encased in a polythene sheath and inserted into the rectum to a depth of approximately 100 mm. Subjects recorded in a daily diary the times when they removed the probe for washroom visits, and the missing temperatures were calculated by linear interpolation. Ambient dry-bulb temperature in the laboratory was recorded every 30 min by a thermocouple array connected to a fixed data logger (MC Systems, Cape Town, South Africa). All thermistors and thermocouples were calibrated, by water immersion, against a quartz thermometer (Quat 100, Heraeus, Hanau, Germany), to an accuracy of at least 0.1°C. The loggers maintain accuracy even in the face of changing environmental temperatures [19].

Before going to bed, the subjects completed a questionnaire describing the events of that day and indicated their evening anxiety on a 100-mm visual analogue scale (VAS), anchored from "terribly agitated" to "utterly calm and peaceful". After each recording night, the subjects assessed the preceding night's sleep quality on a 100-mm VAS with anchor points of "worst possible" and "best ever" sleep. Morning vigilance was rated on a similar VAS with anchor points of "feeling awfully sleepy and lack lustre" and "feeling marvellously alert and energetic".

A 5-ml blood sample was taken from the women between 07:00 and 08:00 hours, after the recording nights. The serum was frozen for later determination of oestradiol and progesterone, using automated chemiluminescent immunoasays (Chiron Diagnostics, East Walpole, Mass., USA). The mean within-assay variation was 7.2% in the oestradiol assay and 6.6% in the progesterone assay. The oestradiol and progesterone assays showed high specificity for these compounds and low reactivity with synthetic oestrogen and progesterone compounds contained in oral contraceptive pills. The cross-reactivity of the oestradiol assay for ethinyl oestradiol was 0.5%, and the cross-reactivity of the progesterone assay for 17α-hydroxyprogesterone was 0.3%.

We excluded 3 of the 12 naturally cycling women from analysis because they did not show an increase in serum progesterone or body temperature in the latter period of their cycles, though they had ovulated in the screening period. One of the women taking oral contraceptives was excluded from analysis because she had only 10% SWS in her active phase and 13% SWS in her placebo phase, which was greater than 2 SD from the mean for the contraceptive group. Data from the remaining nine naturally cycling women (age: 21±4 years; mass: 61.9±8.3 kg; height: 1.66±0.06 m; body mass index: 22.6±2.5 $kg \cdot m^{-2}$) and ten women taking oral contraceptives (age: 22±3 years; mass: 59.3±9.2 kg; height: 1.69±0.07 m; body mass index: 20.8±2.9 $kg \cdot m^{-2}$) were used in the final analysis. The women did not differ significantly in age or in physical characteristics.

Rectal temperature data were smoothed by a 15-min moving average of the 1-min recordings. We then calculated mean 24-h and raw-minimum temperatures. We also determined, from visual inspection of the smoothed temperature curves, the time of the raw-minimum temperature for each individual. If there was more than one temperature minimum of the same magnitude during the night, we took the average time between the minima. We also measured the extent of the nocturnal drop in body temperature for each subject using an index used frequently by thermal physiologists, namely the thermal response index (TRI). In our case, the TRI was the time integral (°C·h), over 7 h, of the change in rectal temperature from that temperature recorded at lights-out (i.e. the area between the actual curve of rectal temperature versus time and a horizontal line drawn through the lights-out temperature).

Statistical analysis

We evaluated sleep over the first 7 h of the recording nights because it was the shortest period for which all subjects were in

Table 1. Rectal temperature (*T*) variables (mean with SD in *parentheses*) for nine naturally cycling women in their mid-follicular and mid-luteal phases, and for ten women taking combined oral contraceptives in their placebo and active phases of the contraceptive pack. (*NS* Not significant, *SNK* Student Newman-Keuls)

Variable	Naturally cycling		Contraceptive		Two-way ANOVA
	Follicular	Luteal	Placebo	Active	
Time of lights-out (hours)	22:57 (18 min)	23:00 (18 min)	23:00 (30 min)	22:56 (39 min)	NS
Time of lights-on (hours)	06:22 (17 min)	06:27 (18 min)	06:39 (28 min)	06:36 (25 min)	NS
Lights-out *T* (°C)	36.9[a,b,c] (0.2)	37.3 (0.3)	37.4 (0.3)	37.5 (0.3)	group effect $F_{1,17}$=9.7, P=0.006; phase effect $F_{1,17}$=23.3, P=0.0002; group/phase $F_{1,17}$=5.6, P=0.03
Mean 24-h *T* (°C)	37.1[a,b,c] (0.1)	37.4 (0.2)	37.4 (0.2)	37.4 (0.1)	group effect $F_{1,17}$=5.9, P=0.03; phase effect $F_{1,17}$=45.1, P<0.0001; group/phase $F_{1,17}$=16.6, P=0.0008
Minimum *T* (°C)	36.3[a,b,c] (0.2)	36.8 (0.1)	36.8 (0.3)	36.9 (0.2)	group effect $F_{1,17}$=12.0, P=0.003; phase effect $F_{1,17}$=36.9, P<0.0001; group/phase $F_{1,17}$=18.5, P=0.0005
Time of minimum nocturnal *T* (hours)	01:11 (115 min)	03:30[d,e] (123 min)	00:51 (66 min)	01:06 (65 min)	group effect $F_{1,17}$=5.8, P=0.03; phase effect $F_{1,17}$=8.2, P=0.01; group/phase $F_{1,17}$=5.3, P=0.03
Thermal response index (°C·h)	–2.4 (1.1)	–2.0 (1.4)	–2.9 (1.7)	–3.0 (1.1)	NS

[a] Significantly different from naturally cycling women in luteal phase, SNK P<0.0005; [b]significantly different from women taking oral contraceptives in active phase, SNK P<0.0005; [c]significantly different from women taking oral contraceptives in placebo phase, SNK P<0.0005, [d]significantly different from naturally cycling women in follicular phase, SNK P=0.002; [e]significantly different from women taking oral contraceptives, SNK P<0.004

bed. The subjective VAS measurements (in mm) were normalized before statistical analysis through the arcsin transform. We investigated differences in temperature, subjective and objective sleep measures, using a repeated-measures two-way ANOVA at a 95% confidence interval, according to study group or menstrual/contraceptive phase. When appropriate, the Student-Newman Keuls post-hoc test (SNK) was used to identify the origins of any differences. Values are given as means ±SD.

Results

The naturally cycling women had significantly different oestrogen (group: $F_{1,17}$=62.6, P<0.0001; phase: $F_{1,17}$=9.9, P=0.006; group-phase: $F_{1,17}$=13.1, P=0.002) and progesterone (group: $F_{1,17}$=76.1, P<0.0001; phase: $F_{1,17}$=84.6, P<0.0001; group-phase interaction: $F_{1,17}$=83.9, P<0.0001) concentrations between menstrual cycle phases, and compared to the women taking oral contraceptives. As expected, serum progesterone (35±12 nmol/l) and oestrogen (520±130 pmol/l) concentrations were higher in the luteal phase than during the follicular phase (progesterone: 2±1 nmol/l; oestrogen: 230±200 pmol/l) (SNK: P<0.001), in the naturally cycling women. The women taking oral contraceptives had oestrogen (58±66 pmol/l) and progesterone concentrations (1.8±0.6 nmol/l) in the active phase that were the same as those during the placebo phase (oestrogen: 79±74 pmol/l; progesterone: 1.7±0.6 nmol/l), and which were significantly lower than those in the naturally cycling women in both menstrual phases (SNK: P<0.04). The serum hormone concentrations in the women taking contraceptives reflect only endogenous progesterone and oestrogen concentrations since the assays that we used did not detect synthetic hormones.

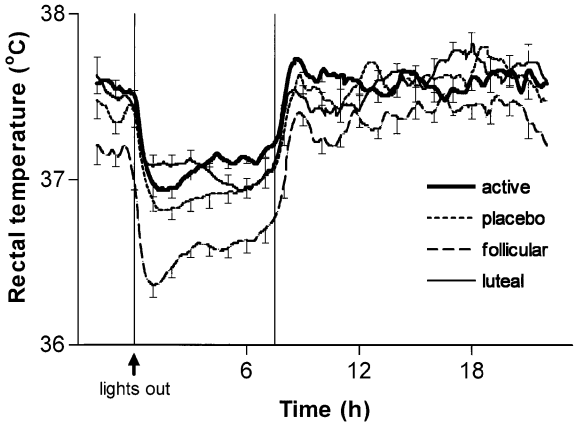

Fig. 1 Mean (*bar* =SEM) rectal temperatures for 24 h from 2 h before lights-out in ten women taking combined oral hormonal contraceptives in the placebo and active phases of the contraceptive regime, and in nine naturally cycling women in the mid-follicular and mid-luteal phases of their menstrual cycles. *Vertical lines* indicate average time in bed

Figure 1 shows the average smoothed rectal temperature curves of the women for 2 h before lights-out and 22 h thereafter. The women elected to go to bed and woke up at similar times (Table 1). They all showed a drop in temperature after lights-out, and a marked rise in temperature after lights-on. As expected, the naturally cycling women had significantly raised body temperatures, with higher mean 24-h, lights-out, and minimum

Table 2. Sleep variables (mean with SD in *parentheses*) during 7 h of sleep after lights-out for nine naturally cycling women in their mid-follicular and mid-luteal phases, and for ten women taking combined oral contraceptives in their placebo and active phases of the contraceptive pack. (*NS* Not significant, *SNK* Student Newman Keuls)

Variable	Naturally cycling		Contraceptive		Two-way ANOVA
	Follicular	Luteal	Placebo	Active	
Sleep efficiency (%)	94 (2)	93 (2)	94 (3)	95 (2)	NS
Sleep onset latency (min)	14 (7)	11 (8)	11 (7)	11 (7)	NS
Latency to stage 3 (min)	10 (3)	8 (2)	10 (2)	11 (3)	NS
Latency to REM sleep (min)	69 (14)	62 (9)	59 (14)	62 (15)	NS
Stage-2 sleep (%)	40 (3)	39 (5)	43 (3)	48[a,b] (4)	group effect $F_{1,17}$=20.0, P=0.0003; phase effect NS; group/phase $F_{1,17}$=6.1, P=0.02
Slow wave sleep (%)	24 (3)	27[c] (5)	22 (3)	20 (3)	group effect $F_{1,17}$=10.3, P=0.005; phase effect NS; group/phase $F_{1,17}$=3.8, P=0.07
REM sleep (%)	22 (2)	21 (2)	22 (5)	21 (3)	NS
Awake, movement, and stage 1 (%)	11 (3)	10 (3)	10 (4)	9 (3)	NS

[a] Significantly different from women taking oral contraceptives in placebo phase, SNK P=0.02; [b]significantly different from naturally cycling women, SNK P<0.001; [c]significantly different from women taking oral contraceptives, SNK P<0.01

temperatures in the luteal phase compared to the follicular phase (Table 1). In contrast, the women taking oral contraceptives had similar body temperatures throughout the 24-h recording period in the active phase and in the placebo phase, and their temperatures were similar to those of the naturally cycling women in the luteal phase (Table 1). The naturally cycling women in the follicular phase and the women taking oral contraceptives all reached their minimum temperature soon after lights-out (Table 1), after which their body temperature gradually increased. The naturally cycling women, however, had a delayed onset of their minimum temperature in the luteal phase compared to the follicular phase and the contraceptive group of women (Table 1). Average TRIs over the first 7 h of sleep did not differ between the women, indicating that integrated body temperature dropped to the same extent during the night, regardless of oral contraceptive use or menstrual cycle phase.

There were no significant differences in subjective ratings of evening anxiety, sleep quality or morning vigilance between the two study groups and the two menstrual phases. Before going to bed, subjective assessments of anxiety were the same in the naturally cycling women in their follicular (77±19 mm) and luteal (67±25 mm) phases, and the same in the women taking oral contraceptives in the placebo (65±11 mm) and active (68±16 mm) phases (phase effect: $F_{1,17}$=0.3, P=0.6; group-phase: $F_{1,17}$=1.7, P=0.2). Levels of evening anxiety did not differ between the two groups of women either (group effect: $F_{1,17}$=0.9, P=0.3). Subjective ratings of sleep quality were the same in the follicular (61±17 mm) and luteal (72±12 mm) phases in the naturally cycling women, and in the placebo (70±12 mm) and active (65±20 mm) phases in the women taking oral contraceptives (phase effect: $F_{1,17}$=0.6, P=0.4; group effect: $F_{1,17}$=0.05, P=0.8; group-phase: $F_{1,17}$=2.7, P=0.1). Similarly, ratings of morning vigilance were the same in the naturally cycling women in the follicular (59±17 mm) and luteal (66±9 mm) phases, and in the women taking oral contraceptives in the placebo (61±20 mm) and active (67±13 mm) phases (phase effect: $F_{1,17}$=2.4, P=0.1; group effect: $F_{1,17}$=0.1, P=0.8; group-phase: $F_{1,17}$=0.04, P=0.8).

Total time spent in bed was the same in the naturally cycling women in their follicular (445±21 min) and luteal (441±35 min) phases, which was the same as in the women taking hormonal contraceptives (placebo: 453±15 min; active: 452±9 min) (phase effect: $F_{1,17}$=0.2, P=0.6; group effect: $F_{1,17}$=1.3, P=0.3; group-phase: $F_{1,17}$=0.1, P=0.7). Table 2 shows sleep variables for the first 7 h after lights-out for the women. Sleep efficiency was similar for the first 7 h of sleep in all the women on all recording nights (Table 2). Figure 2 shows the percentage of time that the women spent in SWS, stage-2 sleep and REM sleep on their recording nights. The naturally cycling women tended to have more SWS in the luteal phase compared to the follicular phase (SNK P<0.1), and had significantly more SWS compared to the women taking oral contraceptives (Table 2). The women taking oral contraceptives, on the other hand, had significantly more stage-2 sleep in the active phase compared to the placebo phase, and compared to the naturally cycling women (Table 2). REM sleep percentage was the same in all the women regardless of hormonal status. There were no differences between the two groups of women, or between recording phases, in SOL or in time spent awake, moving and stage-1 sleep.

Discussion

We have found that young women using oral contraceptives have body temperature and sleep patterns that differ from those in naturally cycling women. Body temperature was raised throughout 24 h in the women

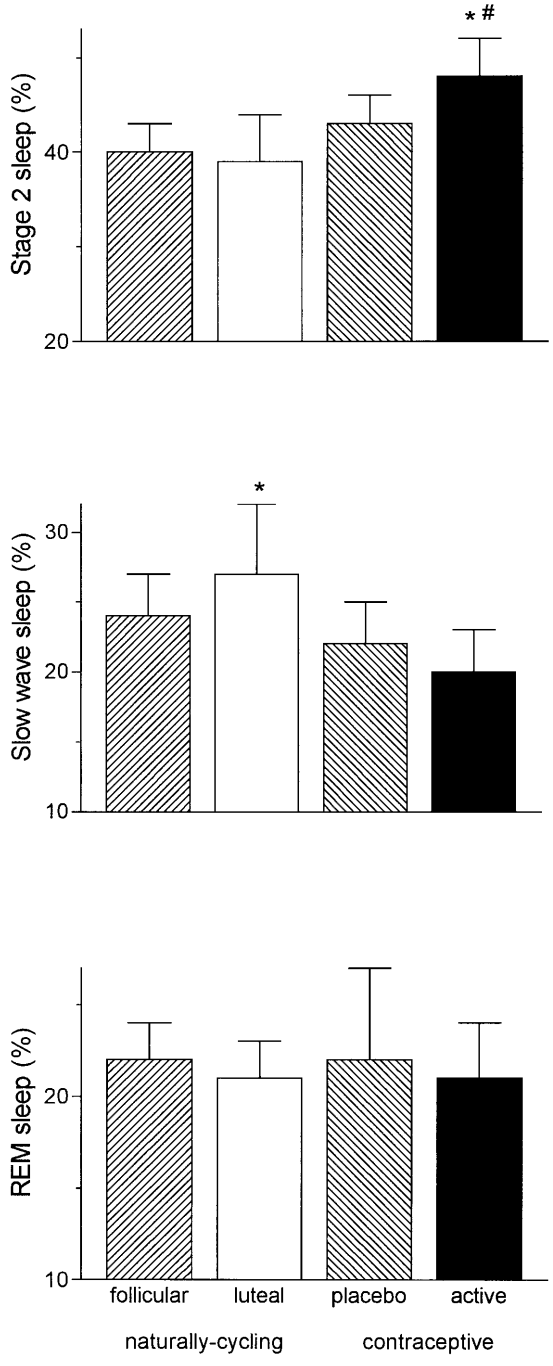

Fig. 2 Percentage of stage-2 sleep, slow wave sleep, and rapid eye movement (*REM*) sleep (mean ±SD) during the first 7 h after lights-out for nine naturally cycling women in the mid-follicular and mid-luteal phases of their menstrual cycles, and in ten women taking oral contraceptives in the placebo and active phases of the contraceptive regime. *Significant differences between naturally cycling women and contraceptive users; #significant difference from placebo phase within the group of women taking oral contraceptives (two-way ANOVA and SNK, $P<0.05$)

taking oral contraceptives in the active phase, and in the naturally cycling women in the luteal phase, compared to the follicular phase. We believe that these body temperature elevations are caused by the thermogenic action of progesterone and progestins. However, women taking oral contraceptives in the placebo phase continued to have raised body temperatures, similar to those in the active phase, indicating a prolonged action of synthetic reproductive steroids on body temperature that is not evident in the natural menstrual cycle.

Oral contraceptive use and hormonal changes during the natural menstrual cycle also influenced sleep, independently of body temperature. The women taking oral contraceptives had significantly more stage-2 sleep in the active phase compared to the placebo phase, and compared to the naturally cycling women in both menstrual cycle phases. Naturally cycling women, however, had more SWS in the luteal phase compared to the women taking oral contraceptives, in both their active and placebo phases. Exogenous and endogenous reproductive steroids therefore influenced different components of sleep. There were no differences, however, in REM sleep, sleep efficiency or subjective sleep quality during the night between the two groups of women.

We measured plasma concentrations of endogenous progesterone and oestrogen to confirm the menstrual cycle phase in the naturally cycling women, and to confirm that the women taking oral contraceptives had not ovulated. The assays were unable to measure plasma concentrations of the synthetic progestins and oestrogens in the women taking oral contraceptives. Even though we knew the daily dose of synthetic hormones taken orally by each woman, we could not accurately predict the serum concentrations because of the large variation that exists between individuals in the pharmacokinetics of contraceptive steroids [17]. Others have reported peak plasma concentrations for progestins of between approximately 10 and 20 nmol/l and for ethinyl-oestradiol, of between approximately 2.0 and 2.6 nmol/l [7], between 1 and 2 h after contraceptive pill administration, concentrations (but not necessarily activity) close to that of the natural progesterone but greater than that of natural oestrogen, in our women during the luteal phase. Plasma concentrations of synthetic steroids decline to less than half of the peak concentrations within 20 h [17]. We attempted to reduce variability in synthetic steroids in the group of women taking contraceptives by including only women who had been taking monophasic contraceptive pills, and for at least 4 months before the study, so that a steady hormonal state should have been reached [16].

Our finding that women taking oral contraceptives have a body temperature over 24 h similar to that of women in the natural luteal phase supports findings from previous studies [4, 24,38]. The rise in body temperature during the luteal phase in naturally cycling women has been attributed to progesterone: body temperature increases approximately 24 h after a detectable increase in progesterone plasma concentration [12], and rapidly falls within 24 h during the transition from the luteal phase to menstruation, when progesterone and oestrogen levels are dropping [11]. Similarly, synthetic progestins probably caused the raised body temperatures in the women taking oral contraceptives in the active phase [36]. However, we found that body temperature remained

elevated when the women were no longer taking synthetic steroids, which confirms the findings of Kattapong et al. [24], and suggests either a prolonged effect, or an alternative mechanism of action, of synthetic progestins on body temperature control compared to endogenous progesterone. Synthetic progestins have a longer metabolic clearance rate than endogenous progesterone, with an elimination half-life of between 8 and 24 h [7], and even when plasma levels are negligible progestins still may be active in the brain [15], or may be metabolized into neuroactive steroids [34]. Also, progestins have a higher relative binding affinity for the progesterone receptor compared to endogenous progesterone [23]. The synthetic progestins therefore may continue to have a thermogenic effect, either directly or through their metabolites in women taking oral contraceptives even after 3 days of withdrawal. Indeed, progesterone substitution therapy in some postmenopausal women is associated with a hyperthermia that persists several days after withdrawal of treatment [32]. Alternatively, the prolonged body temperature elevation in women taking oral contraceptives in the placebo phase could be a consequence of a reduced temperature-lowering effect of oestrogen: chronic administration of synthetic reproductive steroids may cause the down-regulation of oestrogen receptors in the brain [2]. The mechanism and duration of action of synthetic steroids on thermoregulatory control still need to be clarified.

Continuous measurement of body temperature allowed us to investigate the circadian effects of the menstrual cycle and oral contraceptives in young women maintaining their regular daytime schedules. The naturally cycling women in the follicular phase and the women taking oral contraceptives had similar body temperature profiles over 24 h, with body temperature minima occurring soon after lights-out, as we have found previously [4]. Although the naturally cycling women in the luteal phase also had an initial drop in body temperature after lights-out, they had a second lower temperature trough later in the sleep period, so that the time of the temperature minimum was delayed compared to that in the follicular phase, and that in the women taking oral contraceptives. This finding is in contrast to what we, and some others, have found previously [4, 24,38]. Cagnacci et al. [8], however, found a circadian phase delay in the luteal phase compared to the follicular phase, which they attributed to a dampening of melatonin action in the presence of elevated progesterone. But exogenous progestins in the women taking oral contraceptives did not cause a phase delay compared to their placebo phase, or the follicular phase in the naturally cycling women. In naturally cycling women, the reproductive steroids follow cyclical changes during the menstrual cycle and are likely to influence temperature-regulating systems differently from the synthetic steroids contained in oral contraceptives.

Although body temperature profiles were the same, sleep was different, in the active phase compared to the placebo phase in the women taking oral contraceptives. The women had approximately 12% more stage-2 sleep when taking a synthetic progestin and oestrogen compared to the placebo phase, when the hormones had been withdrawn. As far as we are aware, we are the first to compare sleep in the active and placebo phases in women taking oral contraceptives. Friess et al. [18], however, found a significant increase in stage-2 sleep in young men after a single dose of progesterone compared to placebo. The neuroactive steroids derived from natural and synthetic progestins include allopregnanolone, which enhances the effects of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), by modulating the $GABA_A$ receptor [26]. $GABA_A$ receptor agonists increase EEG activity in the spindle frequency range, with a corresponding increase in stage-2 sleep [18,26]. The enhancement of stage-2 sleep during the active phase in the women taking oral contraceptives, therefore, may be mediated by the neuroactive metabolites of progestin. Friess et al. [18] not only found an increase in stage-2 sleep, but also a decrease in SWS latency and a tendency for reduced slow wave activity and stage-4 sleep, in the young men after a single dose of progesterone, compared to placebo. In the women taking oral contraceptives in our study, however, latency to SWS and SWS were the same in the active and placebo phases. Chronic administration of progestins, and the additional presence of oestrogen in the women taking oral contraceptives, may influence sleep slightly differently from an acute dose of progesterone only; oestrogen modulates the effects of progesterone metabolites on $GABA_A$ receptors [2]. Alternatively, as with body temperature, chronic administration of synthetic reproductive steroids may have a prolonged effect on some aspects of sleep, even though the hormones have been withdrawn.

Progesterone in the luteal phase of the naturally cycling women may have been expected to have a similar effect on sleep as that of synthetic progestins in the women taking oral contraceptives, but this was not the case. The women taking oral contraceptives had significantly less SWS compared to the naturally cycling women in the luteal phase, which confirms recent findings from our laboratory [4], and that of Ho [21]. The women taking oral contraceptives also had more stage-2 sleep compared to the naturally cycling women in the follicular and luteal phases. The contradictory effects on sleep of exogenous progestins in women taking oral contraceptives compared to endogenous progesterone in the luteal phase in naturally cycling women may be a consequence of the greater potency of synthetic progestins compared to natural progesterone [34]. Also, the cyclical variations both in progesterone and oestrogen in naturally cycling women, rather than sustained hormone concentrations in women taking oral contraceptives, may govern the extent of their influence on sleep architecture. Driver et al. [14] found approximately a 10% increase in stage-2 sleep in the early-luteal phase compared to the late-follicular phase, but not when comparing the mid-follicular and mid-luteal phases. Possibly, we did not find a similar enhancement of stage-2 sleep by endogenous progesterone in the natural luteal phase compared to synthetic progestins in the women taking oral contraceptives because we

sampled only in the mid-follicular and mid-luteal phase in the naturally cycling women.

Sleep did not vary significantly during the menstrual cycle, although the women tended to have more SWS in the luteal phase compared to the follicular phase. Ho [21] reported an increase in SWS in the luteal phase, but most previous studies, including earlier studies done in our laboratory, have found no change in SWS [3, 4, 14,28] or slow wave activity [14,22] in the luteal phase compared to the follicular phase. Instead, these studies have found decreased REM sleep [3], decreased latency to SWS [4], decreased ROL [28], or increased stage-2 sleep [14] in the luteal phase compared to the follicular phase. The conflicting findings between studies investigating the influence of the menstrual cycle on sleep may be a consequence of small sample sizes, inter-individual variation and different sampling times during the menstrual cycle. A consistent finding in most studies on sleep in women during the normal menstrual cycle, however, is the preservation of sleep efficiency in the follicular and luteal phases, which we also found in our study. We also can state from our study that women who are taking oral contraceptives maintain a similarly high sleep efficiency to that of naturally cycling women, regardless of their hormonal status or body temperature.

All of the women had relatively short-onset latencies to REM sleep (≅60 min) but none of them showed any indication of depression on the General Health Questionnaire, or any other changes in sleep architecture that have been associated with depression, such as increased REM sleep [6]. Lauer et al. [27] found similarly short latencies to REM sleep in their subjects, which they attributed to their study design, which allowed the subjects to remain relatively inactive between preparations for sleep recordings and lights-out, similar to our study design. REM latencies often are shortened after such a resting period [27].

In conclusion, we have shown that women taking oral contraceptives have persistently raised body temperatures, similar to those of naturally cycling women in the luteal phase. Sleep also was influenced by oral contraceptive use, but independently of body temperature. The chronic administration of exogenous reproductive steroids in young women therefore influences sleep and body temperature, but with separable mechanisms of action, and differently from endogenous hormones.

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