Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring

MARY D. COYNE,1 CHRISTINA M. KESICK,2 TAMMY J. DOHERTY,3 MARGARET A. KOLKA,2 AND LOU A. STEPHENSON2
1Department of Biological Sciences, Wellesley College, Wellesley 02481-8203; 2Thermal and Mountain Medicine Division, and 3Biophysics and Biomedical Modeling Division, US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760-5007

Received 25 February 2000; accepted in final form 18 May 2000

Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring. Am J Physiol Regulatory Integrative Comp Physiol 279: R1316–R1320, 2000.—The purpose of this study was to determine whether core temperature (Tc) telemetry could be used in ambulatory women to track changes in the circadian Tc rhythm during different phases of the menstrual cycle and, more specifically, to detect impending ovulation. Tc was measured in four women who ingested a series of disposable temperature sensors. Data were collected each minute for 2–7 days and analyzed in 36-h segments by automated cosinor analysis to determine the mesor (mean temperature), amplitude, period, acrophase (time of peak temperature), and predicted minimum Tc (Tc-min) for each cycle. The Tc mesor was higher (P ≤ 0.001) in the luteal (L) phase (37.39 ± 0.13°C) and lower in the preovulatory (P) phase (36.91 ± 0.11°C) compared with the follicular (F) phase (37.08 ± 0.13°C). The predicted Tc-min was also greater in L (37.06 ± 0.14°C) than in menses (M; 36.69 ± 0.13°C), F (36.6 ± 0.16°C), and P (36.38 ± 0.08°C) (P ≤ 0.0001). During P, the predicted Tc-min was significantly decreased compared with M and F (P ≤ 0.0001). The amplitude of the Tc rhythm was significantly reduced in L compared with all other phases (P ≤ 0.005). Neither the period nor acrophase was affected by menstrual cycle phase in ambulatory subjects. The use of an ingestible temperature sensor in conjunction with fast and accurate cosinor analysis provides a noninvasive method to mark menstrual phases, including the critical preovulatory period.

METHODS

Physiologists often use daily measurements of morning core temperature (Tc) as a marker to predict different phases of the menstrual cycle. Despite its variability and relative inaccuracy, this method has been used to differentiate the follicular or luteal phases of the menstrual cycle, enabling significant work on temperature regulation (2, 16), fluid volume regulation (9, 15), metabolism (14), and exercise responses (10) to be conducted. Tc monitoring has also been used in fertility assessment (3, 14) to detect impending ovulation. However, the key marker of impending ovulation, a drop in Tc, was only observed in ~50% (7) to 80% (19) of patients studied. In those studies, a single measurement of oral or rectal temperature was taken at fixed times in the morning. However, the combined influence of circadian and menstrual cycles on Tc made it difficult to identify ovulation, because a single temperature measurement was located on the sliding scale of the circadian rhythm.

The purpose of the current study was to determine whether Tc telemetry can be used in ambulatory women to identify menstrual cycle phases. We hypothesized that the sensitivity of Tc telemetry would enable detection of impending ovulation. We present a method whereby we record Tc at 1-min intervals over several days during different phases of the menstrual cycle. This methodology allows us to separate the menstrual cycle and circadian effects on Tc. We also present a methodology and procedure for quick computer analysis of the data. These methods enable us to track the changes in the circadian Tc rhythm and to identify particular phases of the menstrual cycle, such as pre-ovulation. This technology is noninvasive, and the methods appear to be robust enough to withstand the vagaries of the normal lifestyle of ambulatory subjects. Using this methodology, we have been able to confirm both the elevation in mean Tc and the reported (5) decrease in amplitude of the circadian Tc rhythm in the luteal compared with the follicular phase. In addition, we have documented an overall decrease in Tc and the predicted minimum Tc (Tc-min) just before the urinary LH peak.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
work occurred at the two locations. Subjects were nonsmokers; were not taking oral contraception or chronic non-steroidal anti-inflammatory drugs such as aspirin or ibuprofen, or melatonin or herbal supplements; and maintained a regular sleep-wake cycle. The presence of ovulatory cycles was documented by obtaining oral baseline temperatures with a digital thermometer at normal arousal time (usually between 0600 and 0730) for a complete cycle before testing and also during testing. Tc was monitored in each subject under her normal living conditions at four phases of the menstrual cycle (Table 1) by use of a calibrated temperature telemetry pill (Human Technologies, St. Petersburg, FL). The silicone-coated pill was easily swallowed with water and passed through the gastrointestinal tract in an average time of 3 days. A small amount of carbohydrate was eaten to move the pill into the intestines. The pill transmitted the local internal temperature to a receiver/datalogger (FitSense Technologies, Wellesley, MA), which was worn in a padded waist pack.

Data continued to be collected while the subjects showered and dressed, if the receiver was placed within 4 feet of the subject. From our knowledge of the oral temperatures in the previous cycle and from continued monitoring of oral temperature, we attempted to begin data collection on the days noted in Table 1. Each subject received 3–4 precalibrated pills per session. She monitored the receiver for a loss of signal and then ingested another pill while in contact with the receiver; monitored the receiver for a loss of signal and then ingested another pill while in contact with one of the research team. Collection continued for 3–4 days or until the last pill was lost (≤7 days). The receivers stored ≤8 days of data, which were collected each minute. Data were downloaded into an IBM-compatible computer at the end of each session and transferred into Excel files. Subjects tested their urine for luteinizing hormone (LH) each morning and evening with a commercially available test stick (courtesy of Carter-Wallace, Cranbury, NJ) to assess the periovulatory period. Such tests are a semiquantitative indicator of rising and falling urinary LH levels during ovulation.

The Tc data were subjected to cosinor analysis with custom software (8) developed in the MatLab (Mathworks, Natick, MA) programming environment by use of an IBM-compatible computer (>300 MHz). The program works on Excel data files and automatically removes extraneous data (temperatures <35°C and >40°C), codes the sleep periods, calculates the days relative to the LH peak, and compiles the results in Excel worksheets. Filtering the data (1, 2, or 4 h) with fast-Fourier transform had no effect on circadian parameters. Several 24- and 36-h data segments (noon to noon, midnight to midnight, noon ± 18 h, and midnight ± 18 h) were tested. We selected the 36-h segments of the data between noon and ±18 h, because these had the best fit as judged by correlation ($r^2$) values. The program returns 24-h cosine segments for plotting midnight to midnight, as well as the mesor, amplitude, period, and acrophase for each segment. The program also provides the maximum ($Tc_{peak}$) and the $Tc_{min}$ for the cosine curve fit. All parameters were tested for significant differences using a one-way ANOVA for a repeated-measures experimental design. A Student-Newman-Keuls post hoc test was done to determine critical differences between phases.

### Table 1. Data collection times

<table>
<thead>
<tr>
<th>Phase of Cycle</th>
<th>Recording Days Based on a 28-Day Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>4 consecutive days—days 27, 28, and 1, 2</td>
</tr>
<tr>
<td>Follicular phase</td>
<td>3 consecutive days within days 4–9</td>
</tr>
<tr>
<td>Periovulatory phase</td>
<td>4 consecutive days within days 10–18</td>
</tr>
<tr>
<td>Luteal phase</td>
<td>3 consecutive days within days 19–24</td>
</tr>
</tbody>
</table>

### RESULTS

Data were collected from four subjects over 11 menstrual cycles (Table 2). In several cases we missed the periovulatory changes on the first attempt and had to collect during a subsequent cycle. The circadian rhythms in $Tc$ for each subject are graphed in Fig. 1, A–D. The mean $Tc$ for each graph is indicated by the dotted line; however, this value could be biased by the number of observations in each phase of the cycle. Solid horizontal lines at the top of each graph represent the sleep periods. The women in this study maintained a relatively consistent sleep/wake schedule, when one considers the vagaries of normal family life. The shifts in mean $Tc$ and change in amplitude of the circadian rhythm throughout the cycle can be clearly recognized in each of the graphs. On visual inspection, several consistent patterns are evident in the graphs. First, the daily mean temperature (mesor) was higher during the luteal phase than during the follicular phase. Second, the daily amplitudes were damped in the luteal compared with the follicular phase. Third, before the LH peak, the daily $Tc_{min}$ reached its lowest value (nadir). Although $Tc$ maximum values were also suppressed during this phase, these differences were more obvious when we looked at the nadir for each day rather than the peak. Statistically, the mesor ($P < 0.001$) and $Tc_{min}$ ($P < 0.0001$) were significantly higher, and the amplitude was significantly lower ($P < 0.005$) in the luteal phase of the cycle compared with the three other phases (Table 3). The preovulatory phase was notable in that both the mesor ($P < 0.001$) and the $Tc_{min}$ ($P < 0.0001$) were the lowest temperatures seen throughout the cycle (Table 3). There were no differences in the period of the circadian $Tc$ rhythm among the four phases of the cycle. The $r^2$ values in Table 3 are averaged over all of the daily $r^2$ values for 36 h and over all subjects for the given phase. The overall mean ($±$SD) for the $r^2$ values was 0.83 ± 0.1, $n = 72$.

### DISCUSSION

We have described and tested a methodology for recording the circadian core temperature rhythm in ambulatory subjects for extended periods of time. This has been coupled with a fast, reliable method for applying cosinor analysis to the resulting data files. Using these methodologies, we have confirmed the effects of the female reproductive hormones on the mesor and amplitude of the circadian $Tc$ rhythm during the follicular and luteal phases. More importantly, this method

### Table 2. Subject data

<table>
<thead>
<tr>
<th>Subject</th>
<th>S01</th>
<th>S03</th>
<th>S05</th>
<th>S07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35</td>
<td>43</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Ht, m</td>
<td>1.61</td>
<td>1.65</td>
<td>1.64</td>
<td>1.52</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>75.9</td>
<td>72.5</td>
<td>88.4</td>
<td>56.8</td>
</tr>
<tr>
<td>Cycle length, days</td>
<td>29, 29</td>
<td>26, 26</td>
<td>30, 31</td>
<td>29, 30</td>
</tr>
<tr>
<td>LH peak, days</td>
<td>15, 15</td>
<td>17, 21</td>
<td>18, 18</td>
<td>14, 17</td>
</tr>
</tbody>
</table>

LH, luteinizing hormone.
clearly demonstrates the fall in both the mesor and $T_{c\text{-min}}$ 1–2 days before the surge of urinary LH.

Clinically, in fertility studies, a rise in oral morning temperature has been used to confirm ovulation and can also be used to grossly predict a time frame for conception. The present data confirm the rise in mesor and the reported decrease in amplitude of the circadian temperature rhythm in the luteal phase of the cycle, which were based on single 24-h segments of measurement (5, 11, 13). However, the current data indicate that both the rise in mesor and decrease in amplitude are not immediate responses but adjust over a 4- to 6-day time frame, which makes it difficult to pinpoint ovulation.

On the basis of observation of oral temperature, prior evidence suggested that ovulation might be preceded by a drop in $T_c$ (7, 14, 19). More recently a decreased regulated body temperature has been associated with the time of the preovulatory estrogen rise (17) and with estrogen replacement in postmenopausal women (4, 18). The data reported here unequivocally demonstrate a significant decrease in both the mesor and the $T_{c\text{-min}}$ within 1 and sometimes 2 days before the urinary LH surge. This temperature drop occurs about 24–48 h before ovulation, and if measured accurately, could provide an important noninvasive tool for predicting ovulation for fertilization studies.

Although we did not measure the plasma levels of estrogen directly, we predict that the fall in $T_{c\text{-min}}$ just before the urinary LH surge is due to the preovulatory estrogen surge. A good correlation has already been established between increased estrogen levels and lowered core temperature in postmenopausal women (4, 12, 18), and the addition of progesterone to these subjects reversed the hypothermic estrogen effect (12).

Although the transition in circadian $T_c$ rhythm from the follicular to luteal phase may take up to 6 days, the transition from luteal phase to menses is relatively rapid and consistent across subjects. For example, the mesor decreased significantly within 24 h and continued to fall during the next 24 h. In three of the four subjects, the amplitude had increased within 24–48 h.

### Table 3. Summary values for the four phases of the menstrual cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mesor $\pm 1 \sigma$</th>
<th>$T_{c\text{-min}}$ $\pm 1 \sigma$</th>
<th>Amplitude $\pm 1 \sigma$</th>
<th>Period $\pm 1 \sigma$</th>
<th>Acrophase $\pm 1 \sigma$</th>
<th>$r^2$ Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>37.08 ± 0.13</td>
<td>36.60 ± 0.16</td>
<td>0.48 ± 0.06</td>
<td>25.52 ± 1.49</td>
<td>15.56 ± 0.97</td>
<td>0.86</td>
</tr>
<tr>
<td>Preovulatory</td>
<td>36.91 ± 0.11*</td>
<td>36.38 ± 0.08†</td>
<td>0.51 ± 0.02</td>
<td>24.52 ± 1.08</td>
<td>14.92 ± 1.47</td>
<td>0.87</td>
</tr>
<tr>
<td>Luteal</td>
<td>37.39 ± 0.09*</td>
<td>37.06 ± 0.14‡</td>
<td>0.33 ± 0.07‡</td>
<td>24.85 ± 0.74</td>
<td>16.24 ± 0.90</td>
<td>0.82</td>
</tr>
<tr>
<td>Menses</td>
<td>37.20 ± 0.19</td>
<td>36.69 ± 0.13</td>
<td>0.46 ± 0.05</td>
<td>24.35 ± 1.95</td>
<td>15.88 ± 1.13</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Data were compiled from 4 subjects. Mean values of the 2- to 3-day collection period from each subject were averaged for each phase of the cycle: follicular, 2–3 days per subject collected from days 4–9 of the cycle; preovulatory, 2 days per subject, i.e., the 2 days before LH peak; luteal, 2–3 days per subject collected from days 6–8 after LH peak; menses, 2 days per subject, i.e., days 1 and 2 of the cycle. *P < 0.001 vs. follicular; †P < 0.0001 vs. follicular, menses, and luteal; ‡P < 0.0001 vs. follicular, preovulatory, and menses; §P < 0.01 vs. follicular, preovulatory, and menses.
as well. This rapid and clear transition that takes place when both estrogen and progesterone levels are dropping is in contrast to the complex interactions and changes seen during the transition at ovulation.

In studies in which ambient light, eating schedules, and activity have been controlled, there was a demonstrable delay in the acrophase in the luteal portion of the cycle (5). Although our data suggest this trend, none of the differences in acrophase were statistically significant. This is not surprising, because changes in acrophase are masked in ambulatory subjects (1) and modified by changes in ambient lighting (6). Ambulatory monitoring of Tc with the temperature-sensing pill can be used post hoc to identify characteristics of changing menstrual cycle phases in individual women. Although measurements of morning oral temperature have been useful for gathering general patterns, there is a great deal of variability, because the core temperature is rising rapidly from its nightly nadir. Consequently, differences in measurement time of 1–2 h can substantially alter the measured temperature and mask important changes in Tc, such as those associated with ovulation.

Regarding the analysis method, although it is based on the cosinor analysis, which has been used extensively for biological rhythm studies, we were able to test the effects of using different data segments and different levels of data filtration. From a qualitative analysis of these results, we found that the best analysis of circadian variability is to use data from 1800 of one day through 1800 on the next day to 0600 of the following morning (a total of 36 h). This provides enough data to fit both the peak and the nadir of the 24-h period adequately. We also found that filtering the data before running the cosinor analysis had little or no effect.

In summary, we propose that the use of an ingestible temperature-sensing pill in conjunction with automated cosinor analysis is an effective tool in evaluating circadian Tc rhythms in human subjects. It is particularly effective in identifying the preovulatory decline in Tc and Tc-min. In addition, we are impressed that the effects of the female reproductive hormones on the circadian pattern of Tc rhythms are so robust that the pattern can be easily quantitated in ambulatory women who are not subjected to controlled lighting, sleep/wake patterns, or activity.

Perspectives

During the last 10 years there have been an increased number of investigations into women’s physiology, psychology, and social interactions, but many of these studies are confounded by a lack of the hormonal status of the subjects. Although measuring blood levels of hormones is an ideal solution, it is often difficult to collect samples or, more importantly, the procedure would seriously affect the subject’s performance. The simple technique of swallowing a telemetric pill and analyzing the changes in the subjects’ circadian core temperature rhythm provides a relatively simple, yet accurate, means of assessing cycle phases, i.e., follicular vs. luteal. In addition, it opens up a means of documenting the preovulatory rise in estrogen as evidenced by a decline in core body temperature, and in turn providing an opportunity to investigate phenomena that might be occurring during this critical time in the cycle.

We thank the volunteers for participating in this study, Anjali Rao for data analysis, Robert Wallace for statistical advice, and Carter-Wallace, for supplying the LH test sticks.

This work was supported by the US Army Medical Research and Materiel Command and both the Fiske and Brachman Hoffman Funds, Wellesley College.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Human subjects who participated in these studies have given their free and informed consent. Investigators adhered to Army Regulation 70–25 and US Army Medical Research and Materiel Command Regulation 70–25 on the Use of Volunteers in Research.

REFERENCES


