

Gender influence on jejunal migrating motor complex

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Aytuğ, Necip, Adnan Giral, Neşe İmeryüz, Feruze Y. Enç, Nural Bekiroğlu, Güler Aktaş, and Nefise B. Ulusoy. Gender influence on jejunal migrating motor complex. *Am J Physiol Gastrointest Liver Physiol* 280: G255–G263, 2001.—The role of gender and the menstrual cycle in small bowel motility has not been clearly elucidated. Jejunal motility was recorded with a nasojejunal catheter incorporating five solid-state pressure transducers in ambulatory menstruating women and men of comparable age over 24 h. All women were studied twice, in the early follicular (early-F) and midluteal (mid-L) phases of the menstrual cycle, verified by determining serum levels of gonadal steroids and gonadotropins. The propagation velocity of phase III was slow and the contraction amplitude was high in both menstrual cycle phases compared with men, and these parameters were correlated with serum estrogen levels in the mid-L phase. In the early-F phase, migrating motor complex (MMC) cycle duration during sleep was long compared with other groups and positively correlated with estrogen concentrations, whereas in the mid-L phase MMC cycle duration during sleep was negatively correlated with serum progesterone levels. In all groups, the frequency of phase III contractions was low and the intercontractile interval measured from pressure peak to peak was long during sleep compared with the awake state. Postprandial motility did not display gender difference in any parameter examined. The results demonstrate that the majority of patterns of motility are similar in menstruating women and men, whereas certain aspects of the MMC, most conspicuously propagation velocity and phase III contraction amplitude, differ. We have also documented circadian variation of phase III contraction frequency in both women and men.

circadian variation; menstrual cycle; ambulatory motility; estrogen; progesterone

MOTILITY OF THE SMALL BOWEL is modulated by biological factors such as fasting (13, 15, 17), caloric content of nutrients (25), sleep (12, 17, 20), and aging (14, 17). The role of gender as a modifier of small bowel motility in humans is controversial and has not been studied in depth. The issue is relevant because the definition of intestinal motility aberrations in disease states requires the role of gender to be elucidated (13). Previous studies in healthy subjects of various age groups reported similar intestinal motor activity between

women and men (14, 17). However, an antroduodenal ambulatory study during wakefulness documented shorter migrating motor complex (MMC) periods in women compared with men (32). The aforementioned studies were performed without controlling the menstrual cycle. In a recent study of duodenojejunal motility, women in the follicular phase were found to exhibit motor activity similar to that of men (26). On the other hand, Knight et al. (18) demonstrated attenuated postprandial antral contractile activity in the follicular phase of women compared with men (18).

Ovarian steroid hormones and pregnancy are suggested to modulate electromechanical behavior of the gastrointestinal smooth muscle. Gastrointestinal muscle strips obtained from pregnant mammals (23) or subjected to progesterone administration (6, 19) exhibit decreased contractile response to cholinergic agents and to cholecystokinin. During pregnancy, lower esophageal sphincter pressure is low and orocecal transit is slow (1, 30). In menstruating women the gastric emptying rate of solids (9, 11, 16, 18) and colonic transit are slow compared with those in men of similar age (9). Therefore, it is appropriate to consider the menstrual cycle in the investigation of motility related to gender difference.

The aim of the present study was to investigate the role of gender and the menstrual cycle on jejunal motor activity in a minimally altered physiological setting. We chose to study early follicular (early-F) and midluteal (mid-L) phases to make a comparison of relatively low estrogen secretory state (days 2–6 of follicular phase) with the high estrogen and progestogen secretory state (days 18–24 of luteal phase). Considering that sleep substantially modulates motility (13, 20), we also investigated whether such modulation is operative in the phases of the cycle studied.

METHODS

Subjects. Healthy menstruating women and men were recruited by advertisement to participate in the study. Subjects with a previous history of gastrointestinal symptoms, chronic diseases, or abdominal surgery other than appendectomy were excluded from the study. None of the subjects was

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on any medication. All women had regular menstrual cycles, and none was taking oral contraceptives for at least 3 mo before the study. Except for one woman all female subjects were nulliparous, and none of them was lactating during the study.

The institutional ethics committee approved the study protocol, and written informed consent was obtained from each subject. Women were fully informed about the consequences of contraception and were advised to refrain from sexual intercourse or to use condom contraception during the study period. All women reported regular menstrual bleeding after the study.

Measurement of jejunal motility. Jejunal pressure events were recorded using a nasojejunal catheter (OD 4.7 mm; Konigsberg Instruments, Pasadena, CA) incorporating five radiopaque solid-state pressure transducers. When properly placed in the jejunum, the proximal transducer was situated at the duodenojejunal flexure and the others were 2, 4, 14, and 24 cm distal to the proximal transducer (designated as *sensors 1–5* starting at the duodenojejunal flexure). Pressure was sampled at a rate of 5 Hz from each transducer and was stored in digital form within a portable 4-MB data logger (Super Logger, Sandhill Scientific, Highlands Ranch, CO). The data were transferred to a computer for later display and analysis. Before each study, the data logger was linked to a PC and the transducers were calibrated by applying pressures of 0 and 100 mmHg at room temperature.

Study design. Each female subject underwent two 24-h ambulatory jejunal manometric recordings, one during the early-F phase and the other during the mid-L phase of the menstrual cycle. The order of the study was randomized. Day 1 of the menstrual cycle was defined as the first day of vaginal flow. Early-F phase was defined as the period from day 2 to day 6 of the cycle, and the mid-L phase was defined as days 18–24 of the cycle in a 28-day cycle period. The mid-L phase of each woman was calculated by taking into account individual cycle periods and estimating the oncoming first day of the cycle period.

Subjects were not allowed to smoke or consume alcoholic beverages for at least 2 days before and during the study. All subjects were tube naive. On the examination day, the subjects fasted after a light breakfast and the intubation of the jejunum began at 3 PM. The recording catheter was placed transnasally into the stomach after topical anesthesia with 1% lidocaine (Abbot Laboratories) had been applied to the nose and pharynx. The passage of the catheter tip beyond the pylorus was observed using fluoroscopic guidance with a freeze-frame facility. A latex balloon attached to the distal end of the catheter was inflated with 5 ml of air to facilitate migration of the assembly. When the correct position of the catheter was observed, the latex balloon was deflated and the catheter was fastened to the nose with adhesive tape. The subjects went home overnight to get acclimatized to the catheter assembly, and they were asked to fast after 12:00 AM. The next morning, the correct position of the transducers was verified under fluoroscopy, and the recording commenced between 8:30 and 11:30 AM. Ten milliliters of venous blood were obtained from an antecubital vein of the women for determination of serum concentrations of estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). During the study subjects continued their daily activities and avoided strenuous exercise. Caloric and fiber content of meals were standardized (30 kcal·kg⁻¹·24 h⁻¹; 20% protein, 40% carbohydrate, and 40% fat), and they were prepared in the study premises according to the preference of the subject. Dairy products were avoided in case of lactose intolerance. Two standard solid meals were eaten:

lunch between 11:30 AM and 12:30 PM and dinner between 6:30 and 7:30 PM. Lunch consisted of one portion and dinner of two portions of the total calories calculated for each subject. Females consumed a median of 600 kcal (range 440–670 kcal) at lunch and 1,200 kcal (range 880–1,340 kcal) at dinner. The corresponding values for males were 700 kcal (range 580–900 kcal) and 1,400 kcal (range 1,160–1,800 kcal). Subjects ingested water ad libitum with meals, and they refrained from eating and drinking at other times during the study. In the case of thirst, small sips of water were allowed. Most of the subjects ate lunch in the study premises and dinner at home. All subjects went home to sleep and returned the next morning for fluoroscopic verification of correct catheter position. The recording was terminated after 24 h. Gonads were shielded during each fluoroscopic verification, and the total duration of radiation exposure was 2.0 ± 1.0, 2.5 ± 0.7, and 2.5 ± 1.0 min, respectively, in the early-F and mid-L phases and in men.

Each subject kept a written diary of times of meals, water intake between meals, retiring to bed to sleep, awakening, and defecation. Subjects also activated the appropriate event buttons on the data logger to designate the times of their activities on the motility recording. Each subject was asked to estimate the time spent in bed before falling asleep.

Analysis of jejunal manometric data. Patterns of motor activity were analyzed visually and with a validated small bowel motility program to identify individual pressure waves and to calculate the frequency, amplitude, and motility index of contractions (2). A threshold pressure of 10 mmHg and a peak separation of 3.2 s were incorporated into the program for recognition of individual contractions. The respective minimum and maximum duration of a contraction were set at 2 and 9 s. Artifacts appearing in all sensors were recognized visually and were excluded from analysis. For the purpose of analysis, data were grouped into periods of wakefulness and sleep. The sleep period was defined as the moment when the subject retired to bed with the intention to sleep in the evening until the time of waking. The remainder of the recording was identified as the wakeful period. The recordings of women were analyzed by two of the investigators who were unaware of the menstrual phase during which the recording was performed.

The following criteria were used to recognize phases of the MMC: 1) phase I was recognized as motor quiescence characterized by less than three phasic events during a 10-min period; 2) phase II was recognized as irregular phasic events that preceded phase III and occurred at a rate of more than two contractions in 10 min; and 3) phase III was recognized as regular phasic contractions of at least 2-min duration at the maximum rate for jejunum (10–12/min) followed by phase I and migration to distal sensors (17). Phasic events in the distal sensor (*sensor 5*) fulfilling all of the characteristics of phase III except migration were treated as true phase III activity, and recordings of this sensor were used for calculation of percentage contributions of different phases of the MMC. In a few recordings, phasic events with the characteristics of phase III were interrupted by periods of quiescence or irregular activity of <30-s duration (17). If such pressure events culminated in an uninterrupted phase III in the distal leads, this activity front was considered as part of a single phase III; otherwise, they were considered to be separate events. MMC cycle duration was defined as the time elapsed between the commencement of two consecutive phase III activities. An average value to represent MMC cycle duration was obtained from all sensors. Phase II characteristics were studied in recordings obtained from *sensor 4*. The fasting periods before lunch, between lunch and dinner, and after

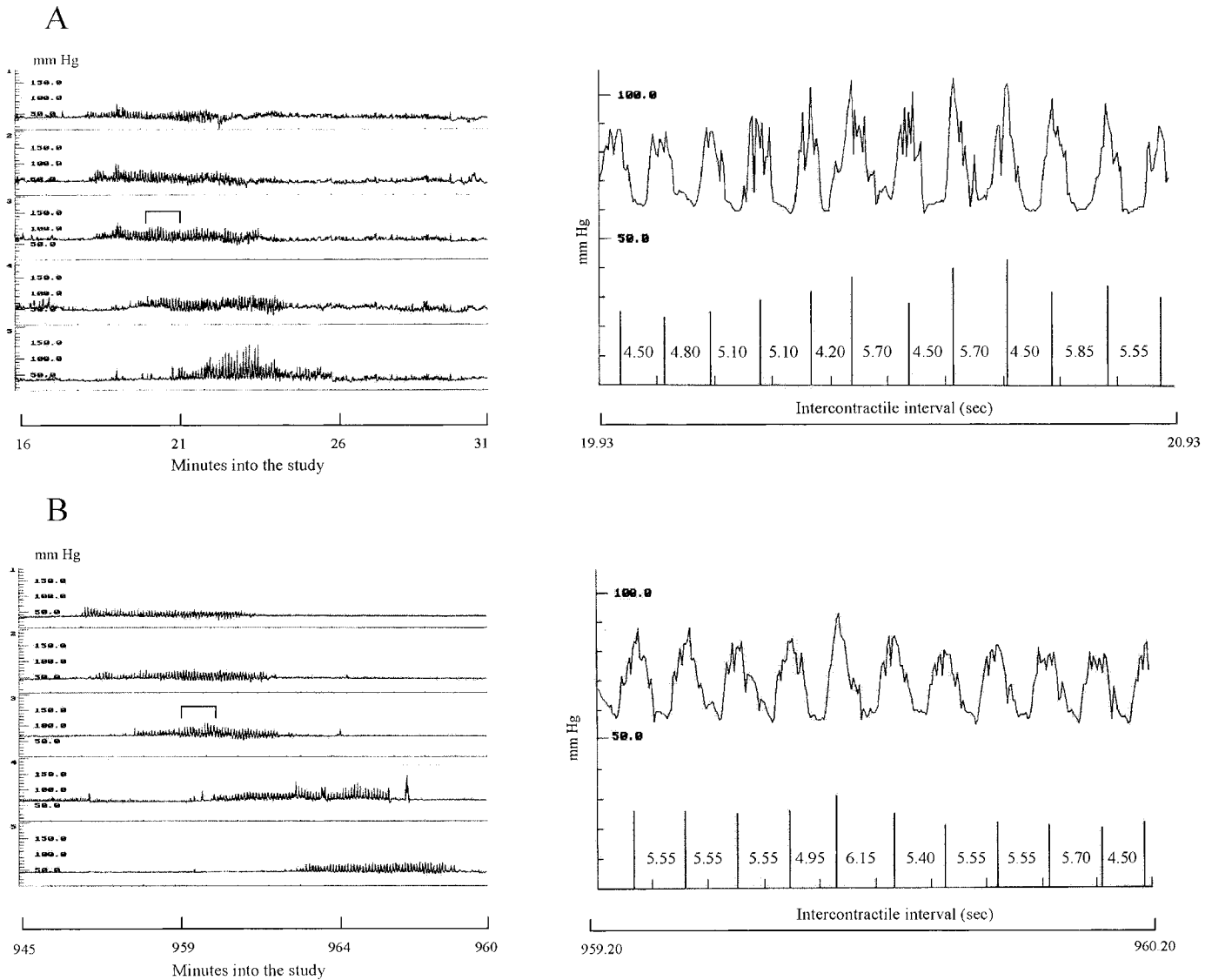


Fig. 1. An example of ambulatory manometric tracing of jejunal phase III during wakefulness (A) and sleep (B) from a woman in the early follicular (early-F) phase of the menstrual cycle. *Sensor 1* was at the duodenojejunal flexure, and the others were distally spaced at 2, 4, 14, and 24 cm from *sensor 1*. Horizontal brackets on the 3rd channels (left) represent 1-min tracings of phase III that are demonstrated on a detailed time scale at right. Vertical bars in right panels represent peak pressure of contraction, and the numbers between them represent intercontractile intervals in seconds.

dinner before sleep were compiled to represent the awake state fasting period. A phase III occurrence was not required for designation of the fasting period before lunch. At other times during the study, a fasting period was defined as the time elapsed from the beginning of a phase III to the beginning of a meal, as recognized by the postprandial motility pattern, or to the termination of the study.

The recordings obtained from the third sensor, which was located ~4 cm distal to the duodenojejunal flexure, were used for analysis of phase III features. The duration, frequency, and amplitude of pressure waves were examined. The temporal features of contractions were examined by calculating the frequency (number of pressure waves/min) and by measuring the intercontractile interval. The intercontractile interval was defined as the time interval between two consecutive computer program-designated contractions measured from pressure peak to pressure peak. Because the beginning

and termination of phase III displayed irregular pressure activity, the middle two-thirds portion of phase III was used for this purpose (Fig. 1). Intervals were measured manually from prints on which 10 mm of paper represented 3 s, using a ruler with 0.5 mm as the narrowest scale. To assess the accuracy of manual reading, a second investigator measured intercontractile intervals without knowing the composition of sample data that were compiled by the unblinded investigator by randomly selecting two phase IIIs in the awake period and two during sleep from the recordings of four subjects in the early-F, mid-L, and male groups. The sample data (793 intercontractile intervals) constituted ~10% of the total intervals measured. The propagation velocity (PV) of a phase III activity was defined as the distance between two pressure sensors spaced 10 cm apart divided by the time taken for the onset of phase III to transverse this distance (cm/min).

Clustered contractions were recognized visually and were defined as 3–10 consecutive contractions occurring at a rate of 10–12/min preceded and followed by a 30-s quiescence (13). The occurrence of clustered contractions during phase II and the postprandial period at *sensor 4* was examined.

The postprandial period was defined as the time interval between the onset of irregular motor activity, as visually recognized and confirmed by subject's diary, to the time when a phase III activity occurred. The postprandial periods after lunch and dinner were analyzed separately. Recordings of the fed pattern were divided into 10-min epochs for computer-assisted calculation of mean amplitude, frequency, and motility index of phasic events. Motility index was defined as all areas under the curve of contractions in the region calculated by the pressure from the baseline times the width on the baseline across the contraction. The calculated data were normalized to a standard unit, minutes ($\text{mmHg}\cdot\text{s}\cdot\text{min}^{-1}$).

Hormone assays. Serum was separated by centrifugation at 4°C and stored at –20°C until assay. Serum concentrations of estradiol and progesterone were determined by solid-phase chemiluminescent enzyme immunoassays (Immulite Estradiol and Immulite Progesterone; Diagnostics Products, Los Angeles, CA). The respective intra-assay coefficients of variation (CV) for estradiol and progesterone assays were 12 and 9%, whereas the respective interassay CV were 13 and 10%. Serum concentrations of LH and FSH were measured by using solid-phase two-site chemiluminescent enzyme immunometric assays (Diagnostics Products).

Statistical analysis. The data are presented as means \pm SD or medians (range) unless stated otherwise. To represent each subject by a single value, a median or a mean was obtained depending on the distribution of the data. Hence the group means represent unweighted means or medians. Comparisons within and between groups were obtained by using paired and unpaired *t*-tests, respectively. Wilcoxon signed-rank test or Mann-Whitney test was used for comparing nonparametric data. For comparison of discrete variables the χ^2 -test with Yates correction as appropriate was used. The relationship between female reproductive hormone concentrations (independent variable) and motility parameters (dependent variable) was estimated by using Pearson's correlation test.

The data representing MMC cycle length and propagation velocity of phase III were analyzed for estimation of variation between and within subjects by using the ANOVA model. The variance components between (s_b^2) and within (s_w^2) subjects were used to estimate the variance within subjects as a percentage of the total variance (V_w): $s_w^2/(s_b^2 + s_w^2) \times 100$ (15).

To estimate the degree of agreement between the two investigators in the measurement of intercontractile interval the "limits of agreement" method was used as described by Bland and Altman (4). Accordingly, the mean difference (\bar{d}) \pm 2 SD displayed by the values of two groups gives the limits of agreement and the 95% confidence intervals indicate the

Table 1. Serum concentrations of hormones

	Early Follicular Phase	Midluteal Phase	<i>P</i> Value
Estradiol, pg/ml	43(23–109)	100(47–190)	<0.01
Progesterone, ng/ml	0.5(0.1–3.6)	10.6(2.3–20.1)	<0.001
LH, mIU/ml	4.2(2.5–9.8)	2.1(0.7–13.1)	NS
FSH, mIU/ml	4.4(2.6–10.9)	1.9(0.6–8.6)	<0.001

Values are medians for ranges indicated in parentheses. LH, luteinizing hormone; FSH, follicle-stimulating hormone; NS, not significant.

Table 2. Duration of fasting and postprandial motor activity

	Early Follicular Phase	Midluteal Phase	Men
Fasting			
Awake	7.1 \pm 1.8	7.1 \pm 1.3	7.8 \pm 1.7
Asleep	7.0 \pm 2.5	7.3 \pm 1.2	7.4 \pm 1.2
Postprandial			
Awake	8.8 \pm 1.8*	8.5 \pm 1.9*	8.4 \pm 1.6*
Asleep	0 (0–6.8)	0.5 (0–2.5)	0.12 (0–1.6)

Values (in h) are means \pm SE except for postprandial asleep values, which are medians for ranges indicated in parentheses. **P* < 0.001 vs. duration of postprandial motor activity during sleep.

precision of the estimate. Statistical significance was defined as *P* < 0.05.

RESULTS

Thirty-six menstruating women and twenty-one men agreed to participate in the study. Twenty-five women and ten men were excluded for various reasons such as failure to pass the catheter beyond the pylorus or through the nasal cavity, antral migration of the catheter, inappropriate serum female gonadal hormone levels for the menstrual phase to be studied or irregular menses, and equipment failure. Hence, 11 menstruating women (mean age 22.0 \pm 2.9 yr) and 11 men (mean age 22.0 \pm 3.3 yr) completed the study. The mean duration of the menstrual period in the female study groups was 28.5 \pm 1.7 days. Thus mid-L phase was studied during days 19–24 of the menstrual period. Mid-L phase was the first study in seven women. The two studies were separated by a median of 20 days, and the range was 7–167 days.

The respective median serum estradiol and progesterone levels in the mid-L phase were 2.1 (0.6–6.1)- and 16 (2.3–56)-fold higher than the respective levels observed in the early-F phase, and all hormone concentrations were within the appropriate ranges of the phases studied (Ref. 21; Table 1). In the mid-L phase, the median serum FSH level was suppressed characteristically for the luteal phase.

The mean recording times of 23.8 \pm 0.4, 23.7 \pm 0.5, and 24.1 \pm 0.4 h in the early-F phase, mid-L phase, and male groups, respectively, were not significantly different from each other. Estimated delay to sleep was ~15–25 min. The quality of sleep was reported generally as good.

Fasting motor activity. The mean duration of fasting motor activity in the awake state was not significantly different between groups or compared with the fasting motor activity during sleep (Table 2).

The respective number of MMC cycles identified in the early-F, mid-L, and male groups were 87, 101, and 110 for the total study period. The proportions of MMC cycles that occurred before lunch, between lunch and dinner, after dinner, and the next day before termination of the recording were similarly distributed between study groups (χ^2 -test; data not shown). One

Table 3. Migrating motor complex cycle duration

	Early Follicular Phase	Midluteal Phase	Men	P Value
Awake				
No. per subject	5(0–5)	3(0–5)*	4(0–10)	NS
Cycle duration, min	45(30–86)†	50(32–77)	45(25–64)	NS
Asleep				
No. per subject	5(0–8)	6(3–8)	6(4–10)	NS
Cycle duration, min	76(45–128)	58(40–80)	55(31–104)	<0.05‡

Values are medians for ranges indicated in parentheses. * $P < 0.001$ vs. midluteal asleep; † $P < 0.02$ vs. early follicular asleep; ‡early follicular vs. other groups.

woman subject had complete MMC cycles only during the mid-L phase while asleep. During sleep the median MMC cycle in the early-F group was longer compared with the mid-L and male groups (Table 3). Within-subject variance of the MMC cycle duration as a percentage of total variance is depicted in Table 4.

Phase III characteristics. The respective numbers of phase IIIs observed in the awake period and during sleep were 143 and 164. The mean phase III duration was similar among groups, and there was no circadian variation (Table 5). The mean amplitude of pressure waves was higher in women during wakefulness, but statistical significance was not observed (Table 5). However, during sleep the respective mean amplitudes of 30.4 ± 4.2 and 31.4 ± 7.2 mmHg in the early-F and mid-L groups were higher than the corresponding value of 25.3 ± 5.9 mmHg in the male group ($P < 0.05$) (Table 5).

In the awake period the mean frequency of phase III pressure waves in all groups was higher than that observed during sleep (Table 5). In the awake period the mean numbers of intercontractile intervals measured were 112 ± 47 , 103 ± 57 , and 138 ± 77 in the early-F, mid-L, and male groups, respectively. These values were not significantly different from each other or from the corresponding values obtained during sleep except in the mid-L group, which contributed fewer data points in the wake state. The mean (\pm SD) intercontractile intervals in the wake state were 5.14 ± 0.23 , 5.18 ± 0.23 , and 5.18 ± 0.21 s in the early-F, mid-L, and male groups, respectively, and these values were shorter than the corresponding values obtained in the sleep period [early-F, 5.29 ± 0.23 s ($P = 0.07$); mid-L, 5.32 ± 0.22 s ($P < 0.05$); male 5.35 ± 0.29 s ($P < 0.01$); Fig. 2]. As described in METHODS, 793 intervals

Table 4. Within-subject variance of migrating motor complex cycle duration as a percentage of total variance

	Early Follicular Phase	Midluteal Phase	Men
Total period	48	60	45
Awake	55	55	77
Asleep	37	63	32*

* $P < 0.04$ significant variation between subjects by ANOVA.

Table 5. Features of phase III recorded at 4 cm distal to duodenojejunal flexure

	Early Follicular Phase	Midluteal Phase	Men	P Value
Awake				
No. per subject	4.3 ± 1.8	$3.7 \pm 1.9^*$	5.7 ± 3.3	NS
Duration, min	4.2 ± 1.0	4.7 ± 1.9	4.2 ± 0.8	NS
Contraction frequency, min^{-1}	$11.0 \pm 0.6^\dagger$	$11.3 \pm 0.5^\ddagger$	$11.2 \pm 0.5^\S$	NS
Amplitude, mmHg	30.4 ± 5.3	30.5 ± 7.2	26.1 ± 7.2	NS
Asleep				
No. per subject	4.5 ± 1.9	5.6 ± 2.8	5.6 ± 2.4	NS
Duration, min	6.1 ± 2.9	6.2 ± 3.7	4.6 ± 1.3	NS
Contraction frequency, min^{-1}	10.7 ± 0.5	10.8 ± 0.6	10.4 ± 0.5	NS
Amplitude, mmHg	30.4 ± 4.2	31.4 ± 7.2	25.3 ± 5.9	<0.05 vs. men

Values are means \pm SD. * $P < 0.01$ vs. midluteal asleep; † $P = 0.06$ vs. early follicular asleep; ‡ $P < 0.01$ vs. midluteal asleep; § $P < 0.001$ vs. men asleep.

were independently measured by two investigators to assess the degree of agreement. The \bar{d} between the two measurements was 0.0385 s, and the majority of data points were within the limits of agreement (-2 SD: -0.298 s; $+2$ SD: $+0.375$ s). The 95% confidence interval (CI) of the mean difference was 0.027–0.050. The degree of agreement appears to be acceptable because the upper limit of 0.027 of the CI is relatively small considering the ~ 5 -s duration of the intercontractile interval. Thus phase III contractions appeared to occur at a slower pace during sleep compared with the awake state. These parameters displayed neither gender nor menstrual phase difference. The frequency distribution of the male group is presented in Fig. 3 as an example of the circadian variation of phase III contraction intervals.

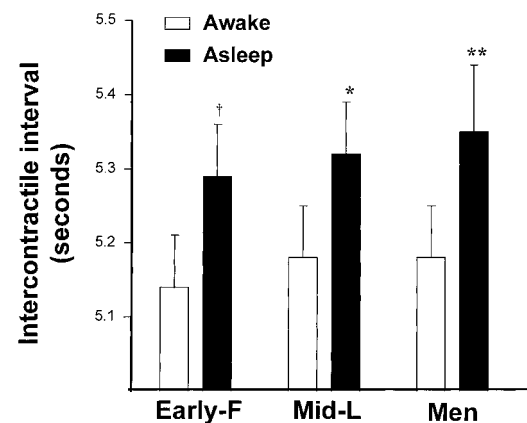


Fig. 2. Intercontractile interval of phase III contractions during the early-F and midluteal (mid-L) phases and in men. The data are derived from recordings of a sensor situated 4 cm distal to the duodenojejunal flexure. The intercontractile interval was the time measured from pressure peak to pressure peak. Data are means \pm SE. During sleep, the intervals were longer compared with the awake state. † $P = 0.07$ vs. early-F awake; * $P < 0.05$ vs. mid-L awake; ** $P < 0.01$ vs. awake men.

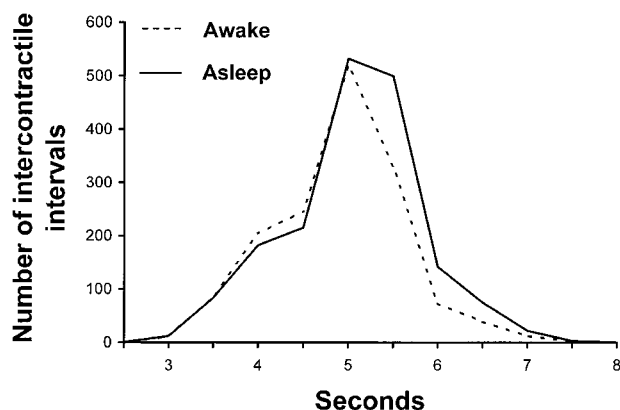


Fig. 3. Frequency distribution of the intercontractile interval of phase III contractions in men. The intercontractile interval was the time interval measured from pressure peak to pressure peak. The frequency distribution curve during sleep is skewed to the right, covering more intervals with longer duration compared with the curve during the awake state.

In each study group, PV between the proximal sensors (*sensors 3 and 4*) displayed a wide range among subjects and the group means were not statistically different from each other both in the awake state and during sleep. On the other hand, PV values measured from the distal sensors (*sensors 4 and 5*) showed a relatively narrow range among subjects in each study group. In the female groups, phase III migrated distally at a slower speed compared with the male group. In the awake state the respective median PV of 5.5 (2.3–8.7) and 4.3 (2.2–10.0) cm/min in the early-F and mid-L groups was slower compared with the velocity of 7.7 (3.8–15.0) cm/min of the male group ($P = 0.07$ and $P < 0.02$, respectively; Fig. 4). During sleep, PV of early-F and mid-L groups were 4.8 (1.6–7.1) and 4.4 (2.3–8.3) cm/min, respectively, and these values were

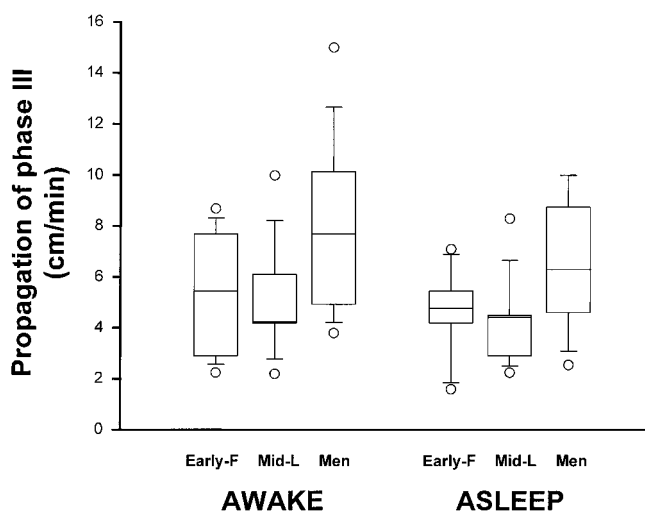


Fig. 4. The propagation velocity of phase III of the migrating motor complex (MMC) recorded in the early-F and mid-L phases of women and men. The data are shown as median values (bars), interquartile range (boxes), ranges, and outliers (○). The median propagation velocities of women were lower compared with those of men (awake: $P = 0.07$ and $P < 0.02$ for early-F and mid-L phases, respectively; asleep: $P = 0.08$ and $P < 0.04$ for early-F and mid-L, respectively).

Table 6. Relative duration of phase I and phase II of migrating motor complex

	Early Follicular Phase (n = 10)	Midluteal Phase (n = 9)	Men (n = 10)	P Value
Awake				
Phase I	22(2–60)*	28(5–60)*	28(4–55)†	NS
Phase II	62(29–96)*	58(22–92)‡	59(39–94)§	NS
Asleep				
Phase I	45(32–87)	59(27–67)	46(16–76)	NS
Phase II	49(5–59)	30(20–62)	44(14–74)	NS

Values (in %) are medians for ranges indicated in parentheses. * $P < 0.01$ vs. early follicular asleep or midluteal asleep; † $P < 0.02$ vs. men asleep; ‡ $P < 0.03$ vs. midluteal asleep; § $P = 0.08$ vs. men asleep.

lower than the 6.3 (2.5–10.0) cm/min value of the male group ($P = 0.08$ and $P < 0.04$, respectively; Fig. 4). There was no statistically significant difference between the values of the female groups and between the values of the awake and asleep states. In comparison with the MMC cycle length, within-subject variance of PV as a percentage of the total variance was of a lesser magnitude in all groups (median 35%, range 21–46%). In the male group variance between subjects was significant ($P < 0.002$ and $P < 0.001$, respectively, for awake and asleep states; ANOVA).

Phase II characteristics. The mean frequency of contractions was higher in the awake state compared with sleep [early-F, 2.5 ± 0.8 vs. 1.5 ± 0.8 /min ($P < 0.01$); mid-L, 3.8 ± 1.8 vs. 2.1 ± 1.3 /min ($P < 0.03$); men, 2.9 ± 1.1 vs. 1.8 ± 0.5 /min ($P < 0.01$)]. The mean contraction amplitude was similar among groups and throughout the study period.

Relative duration of phases I and II of MMC cycle. The occupation of different phases of the MMC cycle calculated as a percentage of the total MMC duration is presented in Table 6. In all study groups, during wakefulness phase I was shorter and phase II was longer compared with the values obtained during sleep.

Postprandial motor activity. Almost all postprandial motor activity occurred while subjects were awake, and the duration of postprandial motor activity was similar among groups, although women and men consumed meals of slightly different caloric content (Table 2). Contraction frequency, amplitude, and motility index did not reveal differences among groups or between dinner and lunch.

Table 7. Frequency of clustered contractions

	Early Follicular Phase	Midluteal Phase	Men	P Value
Awake				
Fasting	1.5(0.9–3.2)	1.7(0.8–3.4)	1.9(0.5–4.5)	NS
Postprandial	1.9(1.3–6.2)*	2.3(0.9–8.4)†	2.2(1.3–4.6)*	NS
Asleep				
Fasting	0.9(0–3.7)	1.1(0.2–3.8)	1.4(0.5–2.3)	NS

Values (no. per hour) are medians for ranges indicated in parentheses. * $P < 0.01$ vs. asleep fasting; † $P < 0.02$ vs. asleep fasting.

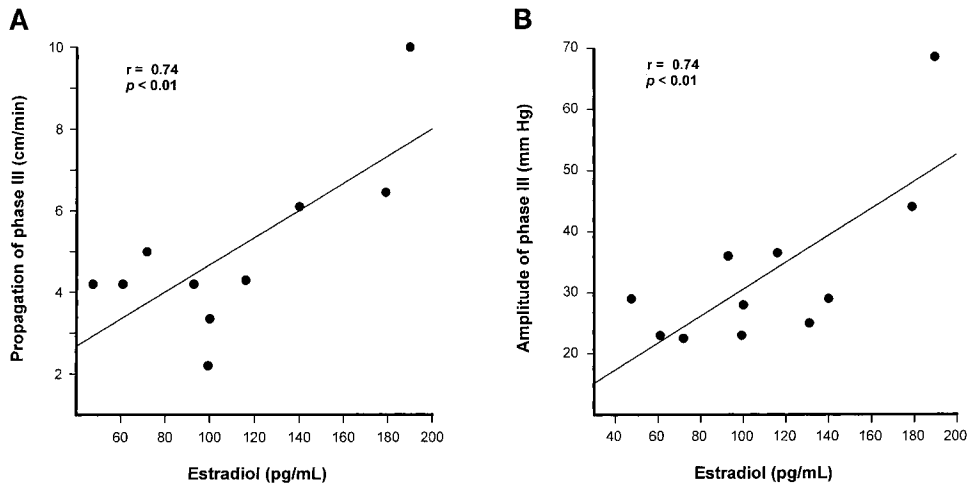


Fig. 5. Relationship between serum estradiol concentrations and propagation velocity (A) and contraction amplitude (B) of phase III during wakefulness in the mid-L phase in women. Serum estradiol concentrations were positively correlated with propagation velocity and contraction amplitude of phase III.

Clustered contractions. The frequency of clustered contractions was similar between women and men during fasting and postprandially. However, in all groups the postprandial frequency was higher compared with that of the fasting asleep state (Table 7).

Correlations between ovarian hormones and motility parameters. In the mid-L phase of the menstrual cycle, propagation velocity of phase III was positively correlated with serum estradiol concentrations. During wakefulness, the correlation coefficient of this association was higher (Fig. 5A) than that found for the total study period ($r = 0.63$, $P < 0.05$). Also in the mid-L phase, phase III contraction amplitude was correlated with estradiol concentrations; again, a stronger association was observed during wakefulness (Fig. 5B) than that for the total study period ($r = 0.69$, $P < 0.02$).

The MMC cycle duration during sleep in the early-F phase was positively correlated with serum estradiol concentrations, whereas the same parameter was negatively correlated with progesterone levels in the mid-L phase (Fig. 6).

DISCUSSION

The results of the present study demonstrate that the majority of the patterns of jejunal motility display

similarity between menstruating women and men, although certain aspects of fasting motor activity are modulated by gender.

The present study has demonstrated for the first time that in menstruating women, particularly in the mid-L phase, PV of phase III is slow compared with that observed in men of comparable age. Similar to the findings of a previous study (15), within-subject variance of propagation was low so that our finding of gender difference is not likely to have resulted by chance. In addition, women displayed higher phase III contraction amplitude than that of men.

According to our findings, menstrual cycle phase did not appear to be the major determining factor for the generation of gender difference in phase III features, because similar findings were observed in women irrespective of the menstrual phase. Nevertheless, correlations between estradiol concentrations and PV or contraction amplitude of phase III were found in the mid-L phase, when circulating levels of female steroids were relatively high, and not in the early-F phase, when both steroid levels were low. Thus estradiol may be the gonadal hormone responsible for the observed gender differences in phase III features. However, because of the complex effects of these female gonadal

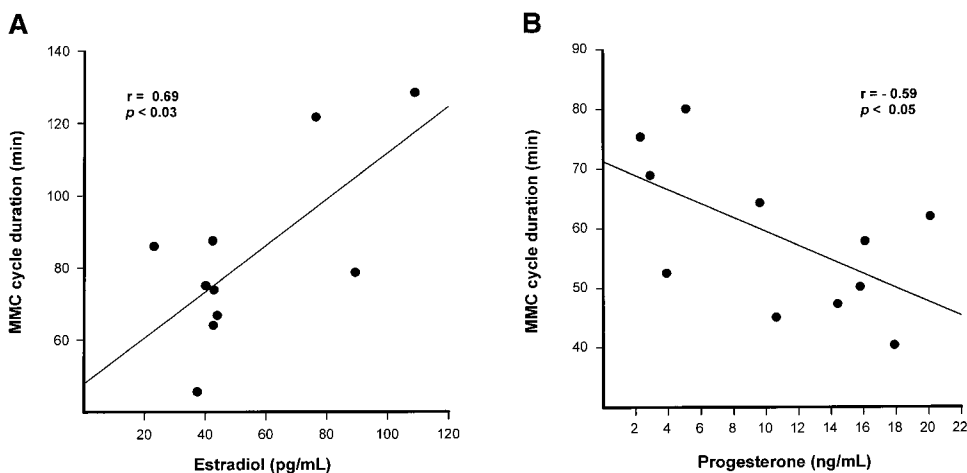


Fig. 6. The MMC cycle duration during sleep was positively correlated with estradiol levels in the early-F phase (A) and negatively correlated with progesterone levels in the mid-L phase (B).

steroids as discussed below and control studies are not available, these correlations cannot be assumed to be on firm ground.

Central, neurohormonal, or myogenic factors that are peculiar to females may be operative in the aforementioned gender differences in jejunal motility. For example, the high contraction amplitude of women observed during phase III and not at other times may be caused by the successive lumen-occluding contractions in an intestinal lumen that is anatomically different from that of men. At the same time, the roles of ovarian hormones on the motility patterns of women cannot be ignored for several reasons. First, the fluctuating levels of female steroids in circulation during the menstrual cycle may not reflect their long-term effects on tissue receptors, particularly because of their genomically mediated actions (28). Second, there are data that demonstrate an influence of female steroids on gastrointestinal smooth muscle. For example, jejunal electromyographic recordings of progesterone-treated mammals demonstrate slower distal propagation of slow waves than that observed in control animals (5), whereas estrogen treatment enhances *in vitro* contractility of the colonic smooth muscle (7). Intestinal transit is slow during the proestrus-estrus phase of the ovulatory cycle of rats (24) and during the luteal phase of humans (29). Furthermore, a mixture of progesterone and estrogen treatment slows gastrointestinal transit (8, 24) and estrogen treatment delays gastric emptying (8).

Furthermore, the actions of ovarian steroids on a variety of tissues including neural tissues appear to be nongenomically mediated as well and include alteration of cell membrane ionic permeability and regulation of cyclic nucleotide turnover and membrane-bound enzyme activity (10, 22). For instance, progesterone reversibly and dose-dependently decreases ionic currents through voltage-sensitive channels in human intestinal muscle cells in a nongenomic fashion (3). Therefore, the effects of female gonadal hormones on jejunal motility may be caused by an interplay of long-term genomic, short-term nongenomic, and up- or downregulatory effects of these steroids on their own receptors (28). Together, ovarian steroids may have a modulatory role in our finding of gender differences in phase III features. Alternatively, as stated above, other factors peculiar to females that are yet to be identified may be also operative.

Similar to previous studies, we have observed that within-subject variance substantially contributes to the total variance of MMC cycle duration (15). According to our findings, MMC cycle duration during sleep in the early-F group is longer compared with the other groups and is positively correlated with estradiol concentrations. On the other hand, MMC cycle length during sleep is negatively correlated with serum progesterone concentrations in the mid-L phase. Prolongation of the cycle duration in the early-F phase may have resulted from estrogen influence because estrogens are the predominant steroids secreted in this phase, and shortening of the cycle duration in the

mid-L phase may have resulted from progesterone influence. However, these findings should be interpreted with caution in light of the high within-subject variance of cycle length, which may have contributed to our findings.

An unexpected and at the same time interesting finding of the present study was the prolongation of intercontractile interval of phase III contractions during sleep. Previous manometric studies, which investigated wave duration and frequency of phase III contractions, did not find circadian variation (12, 31, 32). In an electromyographic study of intestinal slow waves in humans, similar frequencies were found during wakefulness and deep sleep (27). Wave duration measurement has inherent technical difficulties due to the pressure threshold algorithm, and wave duration is independent of contraction frequency and intercontractile interval in a waveform. Our finding may be caused by an unknown technical factor such as sleeving of the intestine over the catheter assembly. However, to fulfill this condition the sleeving would have to occur only during wakefulness. Absence of central nervous system arousal during sleep has been postulated to be responsible for the shortened phase II duration and attenuated phase II contraction frequency (12, 13). The same postulate may be valid for our finding of prolonged contraction interval of phase III during sleep. Alternatively, circadian variation may be the inherent character of neuromuscular tissues, including interstitial cells of Cajal, which serve as the slow wave pacemaking generators within the gastrointestinal tract.

Finally, the frequency of clustered contractions was observed to be similar between women and men. We have also noted that the clustered contraction frequency is higher during the postprandial period compared with during fasting while asleep.

Prolonged ambulatory manometry is being used to define motility patterns that discriminate between disease states and normalcy (13). The present study documented the varying and unvarying aspects of ambulatory jejunal motility in healthy menstruating women and men. In addition, we have documented circadian variation of phase III contraction frequency that did not display gender difference.

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REFERENCES

1. **Baron TH, Ramirez B, and Richter JE.** Gastrointestinal motility disorders during pregnancy. *Ann Intern Med* 118: 366–375, 1993.
2. **Benson MJ, Castillo FD, Wingate DL, Demetrakopoulos J, and Spyrou NM.** The computer as referee in the analysis of human small bowel motility. *Am J Physiol Gastrointest Liver Physiol* 264: G645–G654, 1993.
3. **Bielefeldt K, Waite L, Abboud FM, and Conklin JL.** Nongenomic effects of progesterone on human intestinal smooth muscle cells. *Am J Physiol Gastrointest Liver Physiol* 271: G370–G376, 1996.

4. **Bland JM and Altman DG.** Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 1: 307–310, 1986.
5. **Bortoff A, Morello E, and Mistretta P.** Effect of progesterone and 17-OH-progesterone on intestinal slow wave propagation. In: *Gastrointestinal Motility*, edited by Christensen J. New York: Raven, 1980, p. 387–393.
6. **Bruce LA, Behsudi FM, and Danhof IE.** Smooth muscle mechanical response in vitro to bethanecol after progesterone in male rat. *Am J Physiol Endocrinol Metab Gastrointest Physiol* 235: E422–E428, 1978.
7. **Bruce LA and Behsudi FM.** Increased gastrointestinal motility in vitro following chronic estrogen treatment in male rats. *Proc Soc Exp Biol Med* 166: 355–359, 1981.
8. **Chen TS, Doong ML, Chang FY, Lee SD, and Wang PS.** Effects of sex steroid hormones on gastric emptying and gastrointestinal transit in rats. *Am J Physiol Gastrointest Liver Physiol* 268: G171–G176, 1995.
9. **Degen LP and Phillips SF.** Variability of gastrointestinal transit in healthy women and men. *Gut* 39: 299–305, 1996.
10. **Farhat MY, Abi-Younes S, and Ramwell PW.** Non-genomic effects of estrogen and the vessel wall. *Biochem Pharmacol* 51: 571–576, 1996.
11. **Gill RC, Murphy PD, Hooper HR, Bowes KL, and Kingma YJ.** Effect of the menstrual cycle on gastric emptying. *Digestion* 36: 168–174, 1987.
12. **Gorard DA, Vesselinova-Jenkins CK, Libby GW, and Farthing MJG.** Migrating motor complex and sleep in health and irritable bowel syndrome. *Dig Dis Sci* 40: 2383–2389, 1995.
13. **Husebye E.** The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. *Neurogastroenterol Motil* 11: 141–161, 1999.
14. **Husebye E and Engedal K.** The patterns of motility are maintained in the human small intestine throughout the process of aging. *Scand J Gastroenterol* 27: 397–404, 1992.
15. **Husebye E, Skar V, Aalen OO, and Osnes M.** Digital ambulatory manometry of the small intestine in healthy adults. *Dig Dis Sci* 35: 1057–1065, 1990.
16. **Hutson WR, Roehrkasse RL, and Wald A.** Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* 96: 11–17, 1989.
17. **Kellow JE, Borody TJ, Phillips SF, Tucker RL, and Haddad AC.** Human interdigestive motility: variations in patterns from esophagus to colon. *Gastroenterology* 91: 386–395, 1986.
18. **Knight LC, Parkman HP, Brown KL, Miller MA, Trate DM, Maurer AH, and Fisher RS.** Delayed gastric emptying and decreased antral contractility in normal premenopausal women compared with men. *Am J Gastroenterol* 92: 968–975, 1997.
19. **Kumar D.** In vitro inhibitory effect of progesterone on extra-uterine human smooth muscle. *Am J Obstet Gynecol* 84: 1300–1304, 1962.
20. **Kumar D, Wingate D, and Ruckebusch Y.** Circadian variation in the propagation velocity of the migrating motor complex. *Gastroenterology* 91: 926–930, 1986.
21. **Leon S, Glass RH, and Kase NG.** Regulation of menstrual cycle. In: *Clinical Gynecologic Endocrinology and Infertility*. Baltimore: Williams and Wilkins, 1989, p. 190–193.
22. **McEwen BS.** Non-genomic and genomic effects of steroids on neural activity. *Trends Pharmacol Sci* 12: 141–147, 1991.
23. **Parkman HP, Wang MB, and Ryan JP.** Decreased electromechanical activity of guinea pig circular muscle during pregnancy. *Gastroenterology* 105: 1306–1312, 1993.
24. **Ryan JP and Bhojwani A.** Colonic transit in rats: effect of ovariectomy, sex steroid hormones, and pregnancy. *Am J Physiol Gastrointest Liver Physiol* 251: G46–G50, 1986.
25. **Schönfeld J, Evans DF, and Wingate DL.** Daytime and nighttime motor activity of the small bowel after solid meals of different caloric value in humans. *Gut* 40: 614–618, 1997.
26. **Soffer EE, Thongsawat S, and Ellerbroek S.** Prolonged ambulatory duodeno-jejunal manometry in humans: normal values and gender effect. *Am J Gastroenterol* 93: 1318–1323, 1998.
27. **Tassinari CA, Coccagna G, Mantovani M, Bernardina BD, Spire JP, Mancina D, Vela A, and Vallicioni P.** Duodenal EMG activity during sleep. In: *The Nature of Sleep*, edited by Jonanovic UD. Stuttgart, Germany: Fischer, 1973, p. 55–58.
28. **Tsai MJ, Clark JH, Schrader WT, and O'Malley BW.** Mechanisms of action of hormones that act as transcription—regulatory factors. In: *Williams' Textbook of Endocrinology*, edited by Wilson JD, Foster DW, Kronenberg HM, and Larsen PR. Philadelphia: Saunders, 1998, p. 55–94.
29. **Wald A, van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, Scott L, and Lester R.** Gastrointestinal transit: the effect of the menstrual cycle. *Gastroenterology* 80: 1497–1500, 1981.
30. **Wald A, van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, Scott L, and Lester R.** Effect of pregnancy on gastrointestinal transit. *Dig Dis Sci* 27: 1015–1018, 1982.
31. **Wilmer A, Andrioli A, Coremans G, Tack J, and Janssens J.** Ambulatory small intestinal manometry. Detailed comparison of duodenal and jejunal motor activity in healthy man. *Dig Dis Sci* 42: 1618–1627, 1997.
32. **Wilson P, Perdakis G, Hinder RA, Redmond EJ, Anselmino M, and Quigley EMM.** Prolonged ambulatory antroduodenal manometry in humans. *Am J Gastroenterol* 89: 1489–1495, 1994.