ORIGINAL ARTICLE

Are There Changes in Gastric Emptying during the Menstrual Cycle?

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Background: The questions of whether gastric emptying of solids and liquids differs in men and women and whether emptying is influenced by the action of sex hormones on gastric smooth muscle remain unresolved. **Methods:** We analysed the gastric emptying of digestible solids (GES), liquids (GEL), and radiopaque indigestible solids (GER) in three groups of healthy volunteers: 50 women in the follicular phase of the menstrual cycle, 50 women in the luteal phase, and 100 men. [^{99m}Tc]-labelled diethylenetriamine pentaacetic acid (DTPA) was used as the radioactive marker for digestible solids, and [^{111}In]DTPA was used as the marker for liquids, to time gastric motility after a solid and a liquid meal. GER was evaluated on a different day in abdominal roentgenograms. **Results:** GES and GEL were slower in women than in men ($P < 0.05$), but GER was similar in the two sexes. However, there were no significant differences in GES, GEL, or GER between women in the follicular and those in the luteal phase, between plasma concentrations of oestradiol and progesterone and the variables used to characterize gastric emptying. **Conclusions:** Evidence of postprandial 'physiologic gastroparesis' was found in women, although no differences were found between men and women in gastric motility during fasting. The rate of emptying was not related to changes in plasma concentrations of sex hormones during the menstrual cycle.

Key words: Gastric emptying; menstrual cycle; sex differences; sex hormones

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Gastroparesis is frequent in women (1), many of whom report dyspeptic symptoms during different phases of their menstrual cycle (2). These symptoms may reflect alterations in gastrointestinal motility related to hormonal changes during the menstrual cycle (3, 4). In vitro studies have found that progesterone, alone or associated with oestrogen, can affect the electric and motor activity of gastrointestinal smooth muscle, decreasing contractile activity in the oesophagus, stomach, colon, and gallbladder (5–7). Studies done in vivo have found that female sex hormones decrease the activity of the lower oesophageal sphincter (8) and motor activity of the small intestine (9). In women hormonal changes during the menstrual cycle, pregnancy, and oral contraceptive treatment have been associated with alterations in contractility in the oesophagus and lower oesophageal sphincter (10, 11), in gastrointestinal transit (12, 13), and in gallbladder motility (14).

However, it is debated whether gastric emptying differs in men and women, and whether such differences are related to sex hormones (4, 15–26). It is difficult to draw conclusions from the few studies that have tried to analyse these issues, because of differences in the design and methods used to measure gastric emptying, and because the phase of the menstrual cycle was not taken into account in many studies. The present study was designed to investigate gastric emptying of digestible (GES) and indigestible solids (GER), and liquids (GEL) in premenopausal women, and to compare the findings with those in age-matched men. In addition, we searched for differences in gastric emptying in the follicular and luteal phases of the menstrual cycle and attempted to relate variables that define gastric emptying with changes in plasma concentrations of oestradiol (oestrogen) and progesterone.

Subjects and Methods

Subjects

We studied 200 volunteers free of digestive symptoms or systemic disease (Table I)—100 premenopausal women (50 in the follicular phase and 50 in the luteal phase of the menstrual cycle) and 100 men, matched for age. None of the participants had antecedents of gastric surgery, alcohol intake of more than 40 g/day, or drug treatment (including oral

Table I. Clinical data for women and men

	Women	Men
n	100	100
Age (years)	31.6 ± 6.8	32.2 ± 9.6
Body weight (kg)	53.2 ± 6.4	73.6 ± 5.5
Body mass index (kg/m^2)	21.5 ± 1.8	23.5 ± 1.4
Percentage patients *H. pylori*-positive	57.0	61.0

Results expressed as mean ± standard deviation.

contraceptives) during the 2 weeks before the study or smoked during the 2 days before the study. In addition, systemic, endocrine, and connective tissue-related diseases were ruled out with appropriate haematologic and biochemical analyses. All subjects had a body mass index within 20–25 kg/m^2. All women had a negative pregnancy test and had a regular menstrual cycle for at last 6 months before the study. Duration of the cycle was 28 ± 4 days, and there were no major symptoms during the menstrual cycle. All subjects gave their written consent to participate in the study, which was approved by the Clinical Assays Committee of the University Hospital of Granada and carried out in accordance with the Declaration of Helsinki.

Methods

All the women had normal ovulatory menstrual cycles, as evidenced by a significant increase ($P < 0.01$) in serum progesterone levels during the luteal phase and the onset of menstrual bleeding at the appropriate time. The women were divided into two groups (follicular and luteal phases) on the basis of plasma concentrations of oestradiol and progesterone. Day 1 of the cycle was defined as the 1st day of menstrual flow (follicular phase, days 7–10; luteal phase, days 18–21). Venous blood was obtained at 0830 h from the women to determine oestradiol and progesterone levels. Each sample was centrifuged at 2500 rpm for 10 min, and the plasma was frozen at −80 °C and stored immediately for later assay. All samples were assayed in duplicate by immunoassay methods (Elecsys Oestradiol and Progesterone Immunoassay, Boehringer Mannheim Co., Indianapolis, Ind., USA). All samples for a given steroid were run in a single assay. The presence of antibody-IgG for *Helicobacter pylori* infection in the gastric mucosa was investigated in all subjects (Helico-G, Porton, Cambridge, UK). Two tests of gastric emptying were done as described below.

Test 1. Gastric emptying of digestible solids (GES) and liquids (GEL). In accordance with a previously described procedure (27), at 0900 h, after an overnight fast of at least 8 h, all participants consumed two scrambled eggs cooked to a firm consistency in a teflon pan; each serving was labelled by injecting 22.3 MBq ^{99m}Tc-labelled diethylenetriamine pentaacetic acid (DTPA). Immediately thereafter each subject drank 60 ml of orange juice labelled with 3.7 MBq ^{111}In-DTPA. The total number of radioisotope counts in the abdominal cavity was recorded; this value was 100% of the food retained in the stomach at time = 0. The solid test meal contained 9.1 g protein, 4.6 g carbohydrates, and 26.3 g fat, equivalent to a 260-kCal meal. Radioactivity emitted by the radioisotopes was measured with an Acticamera-CGR gamma camera connected to an Imag-7300-CGR computer. Acquisition time was 60 sec at 0, 5, 15, 45, 75, and 105 min after ingestion of the test meal, in a 128 × 128-pixel resolution matrix. The pulse height analyser was set at the 140-keV photopeak with a 10% window for ^{99m}Tc, and at 247-keV with a 10% window for ^{111}In. The counts were measured with the subject in the supine (anterior projection) and prono (posterior projection) decubitus position, to avoid attenuation error. The images stored in the computer were observed, and the area of interest, comprising the gastric area, was outlined with the digitalizing system's pencil to determine the number of counts in this area. The geometric mean of the values obtained in anterior and posterior projections was used as the count value. The proportion of the isotope remaining in the stomach was plotted against time as previously described (28). Because the scanning intervals were so long, the fractional solid meal retention values were analysed by using the function $y(t) = 1 - (1 - e^{-kt})^{\beta}$. A power exponential curve was computer-fitted to the proportional gastric emptying data to obtain two representative indices, κ and β, and the $T_{½}$. In this equation, the $y(t)$ factor was the fractional meal retention at time t, κ was the gastric emptying rate in min^{-1}, t was the time interval in minutes, and β was the y-intercept extrapolated from the terminal portion of the curve. The unknown factors κ and β were determined with a non-linear least-square algorithm using the measured fractional meal retention, (t), versus time data (t). The initial delay portion of the curve was characterized by a lag phase index, T_{lag}, which was numerically equal to $\ln \beta/\kappa$, and was the time in minutes when the second derivate of the function became equal to zero. The κ index was an estimate of the rate of emptying or the later rapid phase of the emptying curve; the β index was an estimate of the shape of the curve or the earlier and more gradual phase of emptying. The measures used to analyse the liquid component were $T_{½}$ and the amount of tracer remaining 10 min after the liquid meal was swallowed. Between acquisitions the subjects remained seated but were allowed to move about over a distance of approximately 5 m.

Test 2. Gastric emptying of indigestible solids (IDS). IDS were prepared in accordance with the method previously described (27), from 16 F polyvinyl nasogastric tubing cut into 1-cm pieces that weighed approximately 40 mg each. The pieces were filled with powdered barium sulphate and sealed, and each piece was placed in a gelatin capsule of the type used for pharmaceutical preparations. The total volume of radiopaque IDS released in the stomach after the capsule dissolved was approximately 125 mm^3.

At least 48 h after the digestible solids and liquids test, all participants swallowed 10 IDS capsules with a small amount

Table II. Analysis of the gastric emptying curve of digestible solids (according to the function: $y(t) = 1 - (1 - e^{-kt})^{\beta}$) and liquids, and gastric emptying of indigestible solids

	Women				
	Hormonal menstrual cycle				
	Follicular	Luteal	Overall	Men	*P*
n	50	50	100	100	
Estradiol (pg/ml)	84 ± 12.1	97 ± 11.7	–	–	NS
Progesterone (ng/ml)	1.2 ± 0.5	19 ± 5.2	–	–	<0.01
Solids					
Emptying rate (κ)	−0.019 ± 0.001	−0.060 ± 0.008	−0.039 ± 0.006	−0.013 ± 0.003	NS
β	1.24 ± 0.17	1.33 ± 0.29	1.28 ± 0.22	1.23 ± 0.30	NS
T_{lag} (min)	15.7 ± 2.8	17.8 ± 5.1	16.8 ± 4.1	11.3 ± 3.3	*
$T_{½}$ (min)	60.3 ± 8.6	63.5 ± 9.8	61.9 ± 8.9	51.7 ± 6.4	*
Percentage isotope remaining at 60 min	50.1 ± 6.9	52.2 ± 7.6	51.0 ± 9.1	47.7 ± 7.3	*
Percentage isotope remaining at 105 min (%Tc_{105})	26.2 ± 7.3	28.5 ± 11.6	27.3 ± 9.7	20.2 ± 8.1	*
Percentage isotope remaninig at 120 min	16.4 ± 6.9	19.2 ± 9.8	17.8 ± 10.2	11.2 ± 9.9	*
n of IDS remaining at 4 h	0	0	0	0	—
Liquids					
$T_{½}$ (min)	23.2 ± 7.2	24.6 ± 8.3	23.9 ± 7.9	18.4 ± 6.2	*
Percentage isotope remaining at 10 min (%In_{10})	71.4 ± 9.8	73.5 ± 8.9	72.5 ± 9.2	66.3 ± 8.1	*

Results expressed as mean ± standard deviation.
* = $P < 0.05$ men versus women, men versus women in the follicular phase, and men versus women in the luteal phase.

of water after an overnight fast of at least 8 h. Supine abdominal radiographs were taken 4 h later. IDS remaining in the stomach were counted successfully in 96% of the radiographs; when there was doubt, a lateral radiographic image (12% of the studies) was used to confirm the presence and location of IDS. In 4% of the examinations the location of the IDS in the distal stomach or proximal duodenum could not be unequivocally determined; in these cases an intragastric position was arbitrarily assumed. For all radiologic studies the genital region was shielded with lead. The total radiation received in each study was approximately 0.40 mGy.

All data showed a normal Student's *t* test (for comparisons of two samples). All statistical tests were two-tailed and were evaluated at the 5% level of significance. All results were expressed as means ± standard deviations.

Results

Anti-IgG antibody to *H. pylori* was found in 57% of all women and 61% of all men; there was no difference in the proportion of women in each phase of the menstrual cycle who were positive.

Table II shows the characteristics of GES in all three groups. The values for T_{lag}, $T_{½}$, and percentage Tc_{105} were significantly higher ($P < 0.05$) in women than in men, although κ and β were similar in both sexes. However, there were no differences between the two subgroups of women for any of the five variables for GES (P = NS). The values for gastric emptying of both solids and liquids tended to be lower in the follicular phase than in the luteal phase (P = NS).

The values for GEL, $T_{½}$, and percentage In_{10} (Table II) were significantly lower ($P < 0.05$) in men than in women, but there were no significant differences in these values between the two subgroups of women.

Four hours after 10 IDS were swallowed, no capsules were seen in the stomach in any of the subjects.

We found no correlation between plasma concentrations of oestradiol or progesterone and any of the variables of gastric emptying of solids or liquids.

Discussion

Contradictory results have been published with regard to sex differences in GES and GEL. Several studies found little or no difference between men and women (4, 20, 22, 25, 29–33), whereas others noted that digestible solids (17, 19, 20, 24–26, 33–36) and liquids (17, 20, 21, 36) were emptied more slowly in women than in men. The discrepancies between studies are probably due to differences in the study methods—for example, differences in the caloric value of the test meals, the positioning of the subject in the gamma camera, the percentage of obese subjects, and the number of subjects studied and their age.

The present study was based on the most widely and recognized methods (17, 20, 24, 26, 28), and we excluded overweight subjects and matched men and women for age, as these two characteristics can influence gastric emptying (22, 29, 37). Moreover, our subjects drank less than 40 g alcohol daily and had abstained from drinking for at least 12 h before the study. Under these conditions there is no evidence that alcohol consumption interfered with gastric emptying (38). We found that three of the five variables used here to define GES and all variables that define GEL yielded significantly higher values in women than in men. Our findings

concur with earlier reports (17, 20, 24–26, 33, 36) done with methods similar to those we used.

The possible substrate for this 'physiologic gastroparesis' in women is poorly understood. Some studies claimed that the absence of *H. pylori* infection in women is related to gastroparesis (39), although other researchers do not share this view (40, 41). This infection had similar prevalence in the women and men we studied and thus does not appear to be the cause of gastroparesis in our sample of Spanish women. A possible explanation is that sex hormones may inhibit gastric motility, as experimental studies have shown that progesterone inhibits the smooth gastrointestinal muscle (5–8) and have identified oestrogen and progesterone receptors in the baboon stomach (42). However, the few studies that were designed to determine whether female sex hormones influence gastric motor activity, GES, and GEL have produced contradictory findings. Some have found that GES (18) and GEL (21) were slower in the luteal phase of the menstrual cycle, whereas others have found slower emptying during the follicular phase (20, 26), and still others reported no difference between the two phases (4, 23). In the present study we found no differences in the rates of GES or GEL in the luteal and follicular phases. To avoid a possible source of bias that earlier studies failed to take into account (20, 21, 23, 26), we identified women in each phase on the basis of hormone levels in plasma and thus obviated the influence of anovulatory cycles on these values.

Gastrointestinal transit is reportedly prolonged during the luteal phase and pregnancy (12, 13); however, these findings may reflect that fact that the small intestine is more sensitive than the stomach to sex hormones. This would explain why some studies have found normal gastric emptying during the luteal phase (4, 23). Gastroparesis in women may also be related to antral, pyloric, and duodenal dysmotility, although this link has to date not been established unequivocally (26). Some studies have found that of the variables used to define GES, only lag phase (T_{lag}) was normal in women (25, 26, 35). The pattern of normal lag phase with delayed postlag phase may reflect antral, pyloric, and duodenal dysfunction (43) rather than a disorder located in the proximal stomach. This suspicion is supported by the finding of diminished antral contractility in women when compared with men (26); however, findings of delayed GEL, as in the present study and earlier reports (17, 20, 21, 36), speak against this hypothesis. Parkman et al. (44) found that the postprandial increase in an electrogastrographic variable—dominant slow-wave frequency—was smaller in women than in men and was smaller during the luteal phase than during the follicular phase. According to these authors, this alteration may represent the substrate for reduced antral contractility in women (26), although other studies have failed to document sex differences in antral motility (20, 34). The finding that plasma concentrations of motilin are reduced during pregnancy (45) suggests that sex hormones may interact with other hormones that stimulate gastrointestinal motility.

Indigestible solids leave the stomach during the late postprandial phase, as a result of the potent phase-III motor activity of the myoelectric motor complex (27). We found only one earlier study that compared gastric emptying of IDS in women and men: Madsen (22) studied premenopausal women in the follicular phase and postmenopausal women and reported that gastric emptying of IDS (and small-intestinal and colonic transit) in both groups was similar to that in men. These findings are in agreement with our results and suggest that there are no differences between men and women in fasting antral motility. More sensitive methods such as manometry and electrogastrography may be able to detect sex differences in fasting motility; nonetheless, the existence of such differences does not necessarily imply that they are of clinical significance.

The results of the present study suggest that disorders in gastric emptying are not responsible for the dyspeptic symptoms some women report during the menstrual cycle (2). Nonetheless, sex hormones can produce dysrhythmia (46), which can lead in turn to dyspeptic symptoms (47). We recommend that members of control groups used in studies of gastric emptying be matched for sex with members of the study groups. In contrast, it does not appear necessary to take the phase of the menstrual cycle into account in studies of disorders seen predominantly in premenopausal women, such as anorexia nervosa, bulimia nervosa, or functional dyspepsia.

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