Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy

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Walsh, John W., William L. Hasler, Clark E. Nugent, and Chung Owyang. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. *Am. J. Physiol.* 270 (*Gastrointest. Liver Physiol.* 33): G506–G514, 1996.—Women in pregnancy experience nausea, which correlates with gastric slow-wave rhythm disruption. Mediators of these dysrhythmias were explored. To quantitate slow-wave disruption, eight pregnant women with first-trimester nausea underwent electrogastrography after a 250-kcal meal. Results were compared with nonpregnant women with nausea during a prior pregnancy who received estradiol and/or progesterone to levels of the first trimester of pregnancy. Five pregnant women exhibited dysrhythmias, with increases in combined recording time in tachygastria plus bradygastria, as well as decreases in the percentage of electrogastrography signal power in the normal 3 cycle/min range (cpm), compared with nonpregnant women ($P < 0.05$). Estradiol did not evoke dysrhythmias in nonpregnant women; however, progesterone induced increases in recording time in bradygastria plus tachygastria and increases in bradygastric signal power with corresponding decreases in signal power in the 3-cpm range ($P < 0.05$). With estradiol and progesterone coadministration, an additive effect was observed at 3.3 ± 0.8 h, with increased recording time in bradygastria alone and in bradygastria plus tachygastria with corresponding increases in bradygastric signal power and decreases in power in the 3-cpm range ($P < 0.05$). In conclusion, women with nausea of pregnancy exhibit slow-wave rhythm disruption. Similar dysrhythmias are evoked in nonpregnant women by progesterone alone or in combination with estradiol in doses that reproduce levels in pregnancy. Thus gastric dysrhythmias in pregnancy may be due to a combination of elevated progesterone and estrogen levels.

electrophysiology; gastrointestinal motility

NAUSEA AND VOMITING are common complications of normal pregnancy affecting 50–70% of women in the first trimester (2, 16, 20, 28). The vast majority of women with nausea and vomiting of pregnancy have mild symptoms that are treated with support and the reassurance that spontaneous resolution of symptoms will occur. A small fraction of pregnant women, however, may have such severe episodes that dehydration and electrolyte abnormalities supervene. This condition, termed hyperemesis gravidarum, has been estimated to affect 1 of every 1,000 live births (6).

The most widely accepted theories for the etiology of the nausea of pregnancy involve elevations in hormones known to be produced in great quantities during the first trimester. Estrogens and progesterone, both of which increase markedly during early pregnancy, have been proposed as possible factors, as have other circulating hormones (17, 32). When given exogenously, both agents, especially progesterone, can induce nausea in some women (11). Similarly, nearly all women who develop nausea on oral contraceptives containing estrogen and progesterone also experience nausea during early pregnancy, suggesting a possible common etiology (15, 16).

Under normal conditions, the stomach exhibits a rhythmic electrical depolarization called the slow wave, which regulates the frequency and direction of gastric contractions. Abnormalities in this basal electrical rhythm have been associated with altered gastric motor activity and symptoms of nausea and vomiting. A recent report of 32 pregnant women with first-trimester nausea documented slow-wave rhythm disturbances in 26 women, with abnormally rapid rhythms (tachygastria) in 17 women, abnormally slow rhythms (bradygastria) in 5 women, and absent gastric electrical activity in 4 women (24). Postpartum recordings in six of these women demonstrated normalization of slow-wave rhythmicity. Conversely, pregnant women without active nausea and vomiting do not exhibit slow-wave dysrhythmias (27). The role of hormonal alterations in the production of slow-wave rhythm disruption is unknown.

In the present study the potential humoral mediators of the gastric dysrhythmias of the first trimester of pregnancy were explored. Our first aim was to quantitate the magnitude of slow-wave disruption in early pregnancy. Second, with administration of estrogen and progesterone to levels mimicking the first trimester of pregnancy, we assessed whether either agent alone or both in combination could reproduce the gastric dysrhythmias observed in early pregnancy in healthy nonpregnant women. Through these investigations, we hoped to gain understanding of the pathogenesis of gastric slow-wave disruption during early pregnancy.

MATERIALS AND METHODS

Study Populations

Pregnant women. Eight women (23–38 yr of age) with nausea in the first trimester of pregnancy were referred from the Obstetrics and Gynecology Outpatient Clinic at the University of Michigan Medical Center. All women were in the 7th–11th wk of gestation and had experienced nausea continuously or intermittently for 2 wk before investigation. Furthermore all women reported mild-to-severe nausea within 48 h of study. None of the women had symptoms severe enough to require intravenous fluid administration or inpatient care. None of the pregnant women had a prior history of gastrointestinal illness or gastrointestinal surgery, and none were on medications known to alter gastrointestinal motility or produce nausea at the time of study.

Healthy nonpregnant women. Healthy nonpregnant women (24–42 yr of age) with a history of nausea during a previous pregnancy were recruited through campus-wide advertisement. These women had no history of gastrointestinal diseases or prior gastrointestinal surgery and reported no chronic or intermittent nausea subsequent to their pregnancies. No volunteer was on any medication, including oral or subcutaneous contraceptives, at the time of study.

All studies of pregnant and nonpregnant women were approved by the University of Michigan Institutional Review Board. Informed written consent was obtained from all subjects before their participation in the study. Nonpregnant healthy women underwent a serum pregnancy test within 48 h of participation in these investigations.

Cutaneous electrogastrography. Cutaneous electrogastrography was performed according to the method of Stern and colleagues (30). Subjects were placed in a semirecumbent position in a quiet warm room without visual or auditory distractions. After gentle skin abrasion to enhance electrical conduction, four Ag-AgCl electrodes (Accutac diaphoretic electrocardiogram electrodes, NDM, Dayton, OH) were affixed to the abdomen. The first electrode was placed in the midclavicular line below the left costal margin. The third electrode was placed midway between the xiphoid and umbilicus. The second electrode was placed equidistant between the first and third electrodes. A fourth reference electrode was affixed in the right upper quadrant of the abdomen. Electrodes were connected via direct nystagmus couplers (model 9859, SensorMedic, Anaheim, CA) to a chart recorder for continuous display of the slow-wave activity. Time constants were set at 10 s and high-frequency cutoffs at 0.3 Hz to minimize interference from nongastric signals. Respirations were monitored by a belt pneumograph connected to an indirect blood pressure coupler (model 9863B, SensorMedic) on the chart recorder, and any signals exhibiting clear respiratory artifact were excluded from analysis. The chart recorder was interfaced with a personal computer (model 4DX2–66V, Gateway 2000, N. Sioux City, ND) via an analog-to-digital converter (model DAS-16, Metrabyte, Taunton, MA).

The three channels of electrogastrographic recording were initially analyzed visually to determine which lead provided the signal most free of noise during the postprandial period. This lead was then subjected to quantitative computer analysis. All traces were analyzed in blinded fashion, such that the investigator did not know the volunteer or the test conditions being studied. Signals were digitized at 4 Hz by the analog-to-digital converter and filtered above 15 cycles/min (cpm) and below 0.5 cpm to remove high- and low-frequency noise. Commercially available software (Fourier Perspective III, Alligator Technologies, Fountain Valley, CA) was used to perform power spectral analysis on 4-min segments of recording in the 45-min postprandial period. A running spectral analysis plot of the power spectral analysis data was generated across the frequency range of 0.5–10 cpm at 2-min intervals, such that each successive line in the pseudo-three-dimensional plot represented the mean amplitudes at the different frequencies of the 4-min recording segments acquired every 120 s in overlapping fashion. Data from the power spectral analyses were imported in spreadsheet format to commercially available software (Lotus 1-2-3, release 2, Lotus Development, Cambridge, MA) for detection of gastric slow-wave rhythm disturbances.

Electrogastrographic recordings were analyzed in two distinct manners to detect development of slow-wave dysrhythmias. The first analysis format involved the determination of the dominant slow-wave frequency for each 4-min recording segment in the postprandial period by assessment of the largest signal amplitude from the spreadsheets. If the maximal signal amplitude for a given postprandial 4-min recording segment occurred at a frequency of >2 and <4.5 cpm, the dominant frequency was defined as within the normal 3-cpm range. If the maximal signal amplitude was present at a frequency of >4.5 and <9 cpm, the dominant frequency for that recording segment was defined as tachygastria. The tachygastric index (TI) expressed the percentage of time that the dominant frequency was in the tachygastric frequency range. A dominant frequency of >0.5 and <2 cpm defined bradygastria. The bradygastric index (BI) expressed the percentage of recording time that the dominant frequency was in the bradygastric frequency range. A cumulative dysrhythmic index (CDI) was calculated by summing the tachygastric and bradygastric indexes and represented a quantitative assessment of the total slow-wave rhythm disruption during a particular recording interval. In general, the presence of a dominant bradygastric or tachygastric frequency during a given recording segment was associated with clear evidence of an abnormally slow or rapid slow-wave frequency upon visual analysis of the electrogastrographic trace.

In many regions of the electrogastrographic traces, there was apparent degeneration of the normal 3-cpm activity with no clear dominant frequency. Thus to attempt to detect an increase or decrease in the underlying slow-wave frequency, a second analysis format was employed to quantitate the electrogastrographic signal powers in the bradygastric (>0.5 and <2 cpm), normal (>2 and <4.5 cpm), and tachygastric frequency ranges (>4.5 and <9 cpm). This technique has been previously employed by us and other investigators to detect development of tachygastria and bradygastria (10, 21). To perform this analysis, signal powers in each frequency range were summed in 0.25-cpm increments, divided by the sum of the signal powers from 0.5 to 9 cpm, then multiplied by 100 to give a percent value. Bradygastric, normal, and tachygastric activities were thus expressed as a percentage of total signal power.

Study Design

Gastric dysrhythmias during the first trimester of pregnancy. Pregnant women underwent a single 1-h cutaneous electrogastrographic recording after an overnight fast. On the morning of the study, venous blood was obtained for determination of serum estradiol and progesterone levels during the first trimester of pregnancy. After a 15-min basal recording period, each pregnant woman ingested a 250-kcal liquid nutrient meal (Ensure, Ross Laboratories, Columbus, OH). Electrogastrographic recording was continued in the postprandial state for an additional 45 min. All analyses reported include data from this 45-min postprandial period.

Gastric dysrhythmias with hormone administration in healthy nonpregnant women. Five healthy nonpregnant women with a history of nausea in the first trimester of pregnancy were enrolled in each of three groups. The first group received estradiol (10 mg po; Estrace, Mead Johnson Laboratories, Evansville, IN). The second group received progesterone (1,600 mg via vaginal suppository). The third group received a combination of estradiol (10 mg po) and progesterone (1,600 mg via vaginal suppository). Preliminary studies in healthy women determined that these doses produced serum estradiol and progesterone levels that approximated those of the first trimester of pregnancy.

After an overnight fast, an intravenous catheter was inserted into a forearm vein for serial blood withdrawals. Catheter patency was maintained with periodic infusion of a heparinized flush-lock solution (100 USP U/ml). Venous blood samples were obtained for determination of baseline estradiol

and progesterone levels before study. Baseline electrogastrographic recordings were obtained. After a 15-min basal period, subjects ingested the 250-kcal liquid nutrient meal, and postprandial recording continued for an additional 45 min. The women then received the predetermined study drug(s) and underwent serial electrogastrographic recordings at 1, 3, and 5 h after drug administration. As described above, a 250-kcal liquid meal was ingested 15 min into each recording, and postprandial recordings were obtained during the subsequent 45-min time period. Preliminary studies in our laboratory demonstrated that gastric slow-wave activity returns to basal levels within 90 min after ingestion of the 250-kcal liquid meal. Thus the serial performance of electrogastrographic recordings every 2 h was not affected by prior nutrient ingestions. Venous blood samples were obtained at 1, 3, and 5 h after drug administration for determination of serum estradiol and progesterone levels as a function of time.

Serum estradiol and progesterone determination. Venous blood samples for determination of serum estradiol and progesterone levels were immediately centrifuged, and the serum was frozen and stored at −20°C. A commercially available kit (Diagnostic Products, Los Angeles, CA) was used to measure serum estradiol by a specific radioimmunoassay with ^{125}I-estradiol as standard. Serum (100 μl) was pipetted into tubes coated with antibodies to rabbit estradiol. One milliliter of ^{125}I-estradiol (0.03 μCi/ml) was added to each tube and then vortexed. Samples were incubated for 3 h at room temperature and then decanted. Pellets were counted for 1 min in a gamma counter. The sensitivity of the assay was 8 pg/ml, and the intra- and interassay coefficients of variation were 4–7% and 4.2–8.1%, respectively.

A commercially available kit (Diagnostic Products) was used to measure serum progesterone by a specific radioimmunoassay with ^{125}I-progesterone as standard. Serum (100 μl) was pipetted into tubes coated with antibodies to rabbit progesterone. One milliliter of ^{125}I-progesterone (0.05 μCi/ml) was added to each tube and then vortexed. Samples were incubated for 3 h at room temperature and then decanted. Pellets were counted for 1 min in a gamma counter. The sensitivity of the assay was 0.03 ng/ml, and the intra- and interassay coefficients of variation were 2.6–6.4% and 5.1–10%, respectively.

Statistical Analysis

Results are expressed as means ± SE. Electrogastrographic parameters and serum estradiol and progesterone levels were compared using paired and unpaired Student's *t*-tests. All *t*-tests were two-tailed. $P = 0.05$ was determined to represent statistical significance.

RESULTS

Gastric Dysrhythmias During the First Trimester of Pregnancy

Eight women with nausea in the first trimester of pregnancy were evaluated to determine the magnitude of gastric slow-wave disruption associated with this condition. The mean serum estradiol level in these subjects was 875 ± 205 pg/ml, whereas the mean serum progesterone level was 24.7 ± 2.4 ng/ml (Table 1). Five of the eight pregnant women exhibited gastric slow-wave dysrhythmias during a 1-h electrogastrographic recording. A representative raw electrogastrographic signal and running power spectral analysis from a woman with nausea in the first trimester of pregnancy shown in Fig. 1 demonstrate disruption of normal 3-cpm activity and a predominance of activity in the bradygastric frequency range <2 cpm. As a whole, this group had a mean TI of 17 ± 7 and a BI of 13 ± 6 compared with 8 ± 4 and 6 ± 2, respectively, for the nonpregnant women under postprandial conditions (Fig. 2). A CDI, calculated from the sum of the TI and BI, was significantly greater in the pregnant (30 ± 7) than in the nonpregnant women (14 ± 4, $P < 0.03$) under basal conditions (Fig. 2). Similar results were obtained when the percentages of total electrogastrographic signal power in the bradygastric, normal, and tachygastric ranges were compared in the five pregnant women with dysrhythmias (Table 2). Trends to increases were observed in bradygastric and tachygastric signal power. As a result, the percentage of signal in the normal slow-wave frequency range was significantly reduced in the pregnant women (31 ± 3%) compared with the nonpregnant women (53 ± 1%, $P < 0.05$). Thus the nausea of the first trimester of pregnancy is associated with measurable disruption of gastric slow-wave rhythmicity. That three of the pregnant women did not exhibit gastric dysrhythmias is indicative of the intermittent nature of slow-wave rhythm disturbances during early pregnancy.

Table 1. *Serum estradiol and progesterone levels in nauseated women in the first trimester of pregnancy and nonpregnant women receiving estradiol and/or progesterone*

Subject Group	Estradiol, pg/ml		Progesterone, ng/ml	
	Before	After	Before	After
Pregnant women	875 ± 205		24.7 ± 2.4	
Nonpregnant women				
Estradiol	48 ± 18	2,067 ± 359		
Progesterone			1.0 ± 0.6	18.2 ± 2.5
Estradiol + progesterone	31 ± 8	1,846 ± 243	0.5 ± 0.2	14.3 ± 1.9

Values are means ± SE.

Gastric Dysrhythmias With Hormone Administration in Healthy Nonpregnant Volunteers

Estradiol and progesterone, alone or in combination, were administered to healthy nonpregnant women with a history of nausea during a previous pregnancy to test the hypothesis that gastric dysrhythmias in association with the nausea of pregnancy may be mediated by elevated levels of circulating hormones during the first trimester.

Gastric dysrhythmias with estradiol alone. Five healthy nonpregnant women received estradiol (10 mg po) after they were subjected to cutaneous electrogastrography under basal conditions. After administration of estradiol, the serum estradiol level increased from a baseline of 48 ± 18 pg/ml to a maximum of 2,067 ± 359 pg/ml at 3.0 ± 0.8 h after drug ingestion (Table 1). These values in fact exceed those observed in the pregnant women with nausea in the first trimester. A representative raw electrogastrographic signal and running power spectral analysis from a nonpregnant

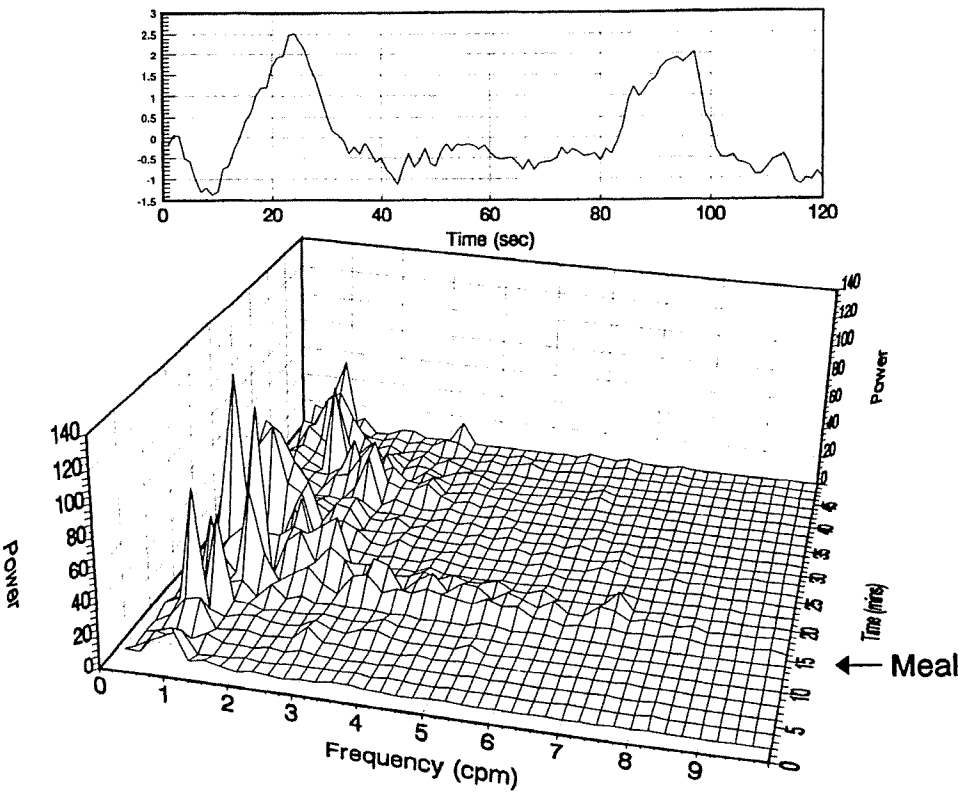

Fig. 1. Sample electrogastrographic results from a pregnant woman with nausea in 1st trimester. *Top*: raw slow-wave signal exhibiting a slow irregular oscillation with a period of >1 min. *Bottom*: power spectral analysis showing frequency distribution of slow-wave signal as a function of time. In this pregnant woman, slow wave exhibits a dominant frequency of 1–2 cycles/min (cpm) before and after (arrow) ingestion of 250-kcal test meal.

woman before drug administration shown in Fig. 3 demonstrate a predominance of normal 3-cpm activity throughout the fasting and postprandial recording periods. Figure 3 also demonstrates the characteristic increase in signal power in the 3-cpm frequency range that occurred in response to ingestion of the test meal. Under basal postprandial conditions, electrogastrographic recordings exhibited a TI of 12 ± 7, a BI of 6 ± 2, and a CDI of 18 ± 6 (Fig. 4). After oral estradiol, postprandial electrogastrographic recordings revealed a maximal TI of 17 ± 8, a maximal BI of 7 ± 5, and a maximal CDI of 24 ± 10 at 3.1 ± 0.6 h after estradiol administration (Fig. 4). These values are not significantly different from the basal levels and do not reach levels observed during the first trimester of pregnancy. Similarly, when electrogastrographic signal powers in the bradygastric, normal, and tachygastric ranges were analyzed, estradiol did not significantly increase activity in either dysrhythmic frequency range (Table 3). Thus oral estradiol administration by itself does not evoke significant gastric slow-wave rhythm disruption.

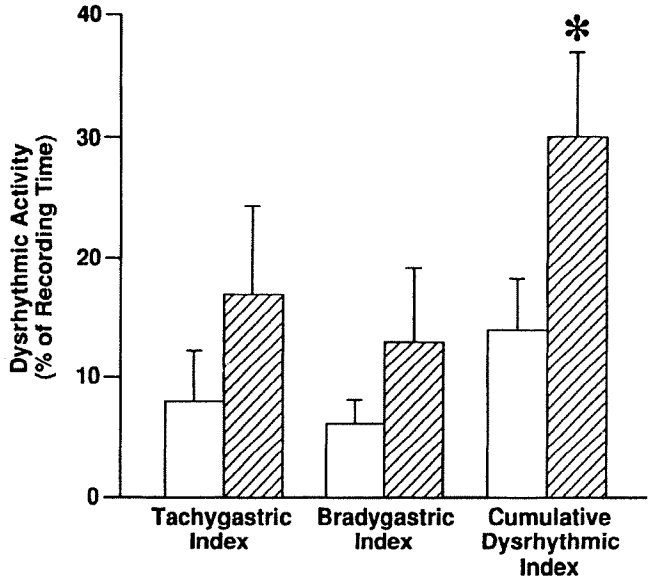

Fig. 2. Dysrhythmic activity in 45-min postprandial period from healthy nonpregnant women (open bars) and pregnant women with nausea in 1st trimester (hatched bars). Trends to increased tachygastric and bradygastric indexes are noted in pregnant women. Values are means ± SE (n = 5). *Significant increase in cumulative dysrhythmic index in pregnant women ($P < 0.03$).

Gastric dysrhythmias with progesterone alone. Five healthy nonpregnant women received progesterone (1,600 mg via vaginal suppository) after they were subjected to cutaneous electrogastrography under basal conditions. After administration of progesterone, the serum progesterone level increased from a baseline of 1.0 ± 0.6 ng/ml to a maximum of 18.2 ± 2.5 ng/ml at 3.8 ± 0.5 h after drug administration (Table 1). This maximal value is not different from that observed

Table 2. *Postprandial electrogastrographic signal powers in bradygastric, normal, and tachygastric ranges in pregnant and nonpregnant women*

Subject Group	Bradygastria	Normal Frequency	Tachygastria
Pregnant women	44 ± 7	31 ± 3*	25 ± 9
Nonpregnant women	34 ± 2	53 ± 1	13 ± 2

Values are means ± SE in percent. *$P < 0.05$, vs. nonpregnant women.

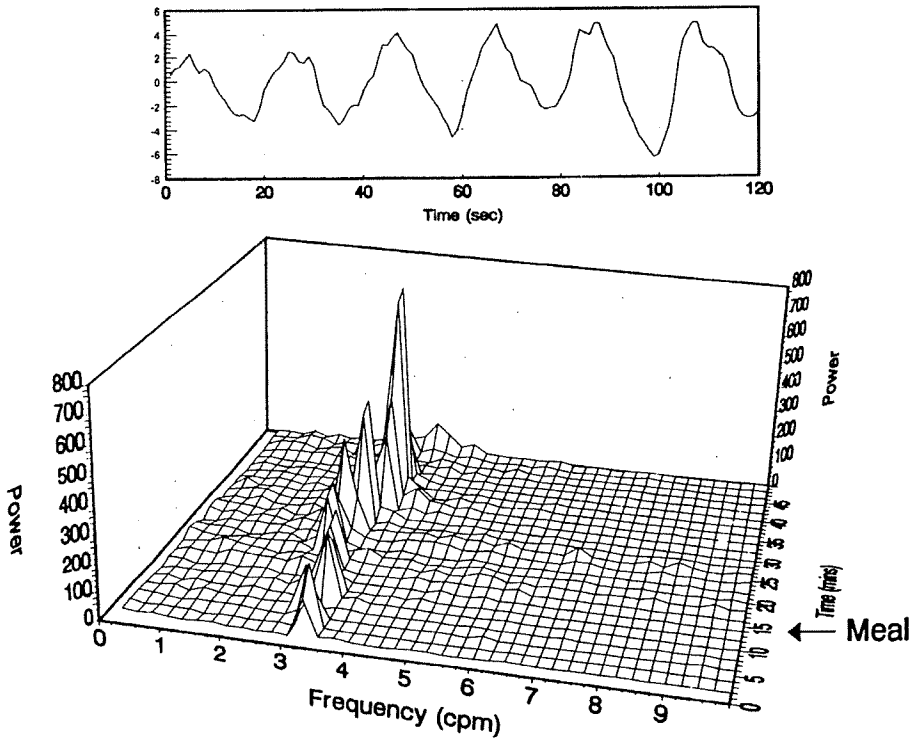

Fig. 3. Sample electrogastrographic results from a healthy nonpregnant woman under control conditions. *Top*: raw signal exhibiting a rhythmic high-amplitude oscillation with a period of ~20 s. *Bottom*: running power spectral analysis showing dominant frequency of ~3 cpm with an amplitude that increases after ingestion of 250-kcal test meal.

during the first trimester of pregnancy. Under basal postprandial conditions, electrogastrography recorded a TI of 7 ± 4 and a BI of 6 ± 3 (Fig. 5). After administration of progesterone, postprandial electrogastrography revealed a maximal TI of 16 ± 5 and a maximal BI of 15 ± 8. The maximal CDI, which occurred 2.2 ± 0.5 h after progesterone administration, was significantly greater (31 ± 8) than under basal conditions (13 ± 6, $P < 0.03$; Fig. 5). Similarly, when signal power percentages in each frequency range were compared, progesterone increased the bradygastric signal percentage from 39 ± 4 to 56 ± 4% ($P < 0.05$), with a corresponding decrease in the percentage of signal in the normal frequency range from 52 ± 3 to 34 ± 3% ($P < 0.05$; Table 3). As with the TI, there was no significant increase in the tachygastric signal percentage. Thus progesterone by itself induces gastric slow-wave rhythm disturbances that are similar in magnitude to those observed during the nausea of the first trimester of pregnancy.

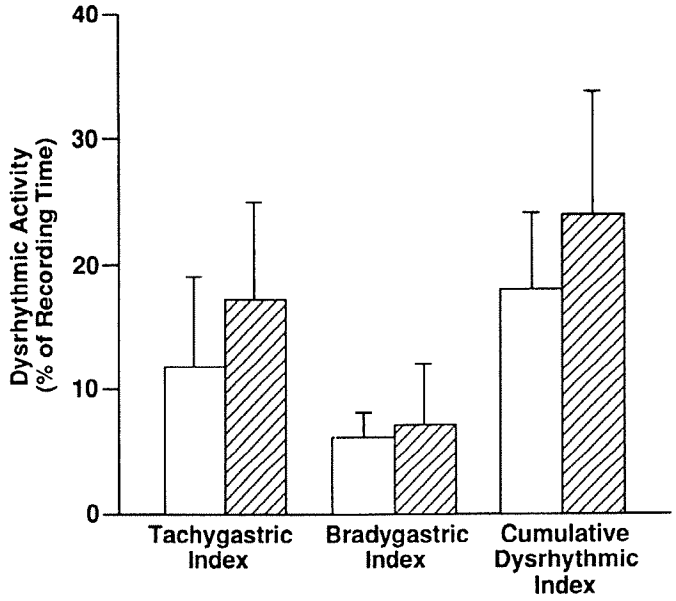

Fig. 4. Dysrhythmic activity in 45-min postprandial period in healthy nonpregnant women before (open bars) and after oral administration of 10 mg of estradiol (hatched bars). Administration of estradiol did not produce significant increases in tachygastric, bradygastric, or cumulative dysrhythmic activity in healthy nonpregnant women. Values are means ± SE ($n = 5$).

Gastric dysrhythmias with estradiol and progesterone in combination. Five healthy nonpregnant women received the combination of estradiol (10 mg po) and progesterone (1,600 mg via vaginal suppository) to evaluate whether estrogen supplementation might potentiate the dysrhythmic effects of progesterone. Coadministration of the two drugs produced an increase in serum estradiol from 31 ± 8 to 1,846 ± 243 pg/ml and an increase in serum progesterone from 0.5 ± 0.2 to 14.3 ± 1.9 ng/ml (Table 1). These values approximate those observed during the first trimester of pregnancy. Under basal postprandial conditions, these women exhibited a TI of 7 ± 5, a BI of 4 ± 2, and a CDI of 11 ± 5 during electrogastrographic recording (Fig. 6). A representative raw electrogastrographic signal and running power spectral analysis obtained from a nonpregnant woman 3 h after administration of the combination of estradiol and progesterone shown in Fig. 7 demonstrate a predominance of signal activity in the bradygastric frequency range. After administration of estradiol and progesterone, the postprandial TI was essentially unchanged (18 ± 13), but there were significant increases in the BI (30 ± 9, $P < 0.01$) and CDI (48 ± 11, $P < 0.01$) at 3.3 ± 0.8 h after drug administration

Table 3. *Postprandial electrogastrographic signal powers in bradygastric, normal, and tachygastric ranges in nonpregnant women before and during estradiol and/or progesterone*

Subject Group	Bradygastria		Normal Frequency		Tachygastria	
	Before	During	Before	During	Before	During
Estradiol	37 ± 4	42 ± 3	50 ± 6	43 ± 4	13 ± 3	15 ± 4
Progesterone	39 ± 4	56 ± 4*	52 ± 3	34 ± 3*	9 ± 2	10 ± 2
Estradiol + progesterone	39 ± 2	63 ± 2*	51 ± 3	25 ± 2*	10 ± 2	12 ± 1

Values are means ± SE in percent. *$P < 0.05$ vs. before drug treatment.

(Fig. 6). The increase in BI after the combination of estradiol and progesterone was significantly greater than the increase after progesterone alone ($P < 0.05$). Similarly, when percentages of electrogastrographic power in the bradygastric, normal, and tachygastric frequency ranges were compared, the combination of estradiol and progesterone had an exaggerated effect on bradygastric activity, with an increase from 39 ± 2% under basal conditions to 63 ± 2% during drug administration ($P < 0.05$; Table 3). This was associated with a corresponding decrease in normal-frequency activity from 51 ± 3 to 25 ± 2% ($P < 0.05$) but no change in tachygastric signal power. Thus estrogen potentiates the dysrhythmic effects of progesterone, suggesting that the complex hormonal milieu present during early pregnancy may be necessary for maximal disruption of slow-wave rhythmicity.

DISCUSSION

In humans, phasic motor activity in the distal stomach is regulated by a pacemaker region in the gastric corpus, which generates a rhythmic electrical oscillation known as the gastric slow wave. Disturbances in slow-wave rhythmicity lead to loss of normal antral phasic contractions (30). If the rhythm is too rapid (tachygastria), the electrical oscillations no longer reach a mechanical threshold for contraction, and gastric atony results. If the rhythm is too slow (bradygastria), the electrical oscillations result in infrequent and irregular contractions (33). Several clinical conditions with nausea and vomiting exhibit gastric slow-wave disruption, either as tachygastria or bradygastria, including diabetic gastroparesis, idiopathic gastroparesis, nonulcer dyspepsia, and motion sickness, suggesting a possible pathophysiological role for gastric dysrhythmias in the induction of nausea in those conditions (8, 22, 23, 29). Recently, Koch and colleagues (23) demonstrated a high prevalence of gastric dysrhythmias in women with nausea in the first trimester of pregnancy. In this study, 26 of 32 pregnant women exhibited slow-wave rhythm disturbances, including 17 with tachygastria, 5 with bradygastria, and 4 with no gastric electrical activity. That pregnancy was the cause of the slow-wave disruption was evident from their observation that gastric dysrhythmias resolved in the postpartum period. The

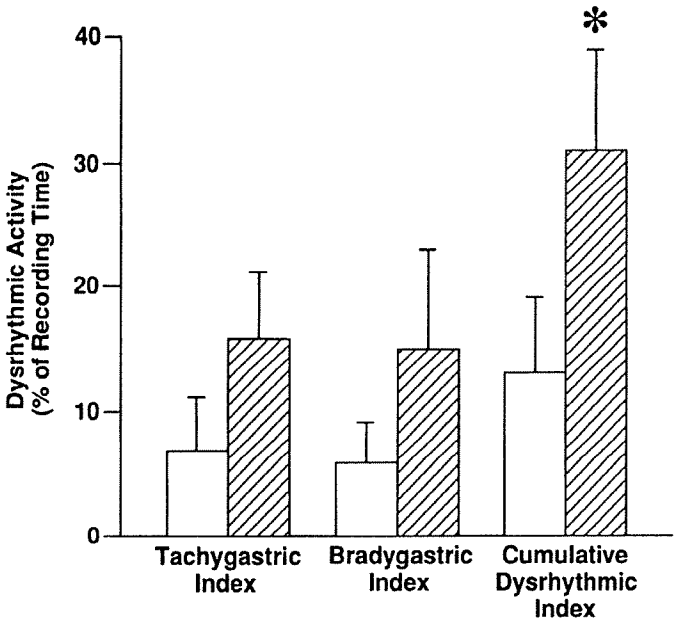

Fig. 5. Dysrhythmic activity in 45-min postprandial period in healthy nonpregnant women before (open bars) and after administration of 1,600 mg of progesterone by vaginal suppository (hatched bars). Administration of progesterone resulted in trends to increases in tachygastric and bradygastric indexes. Values are means ± SE (n = 5). *Significant increase in cumulative dysrhythmic index of magnitude similar to that in pregnant women with nausea in 1st trimester ($P < 0.03$).

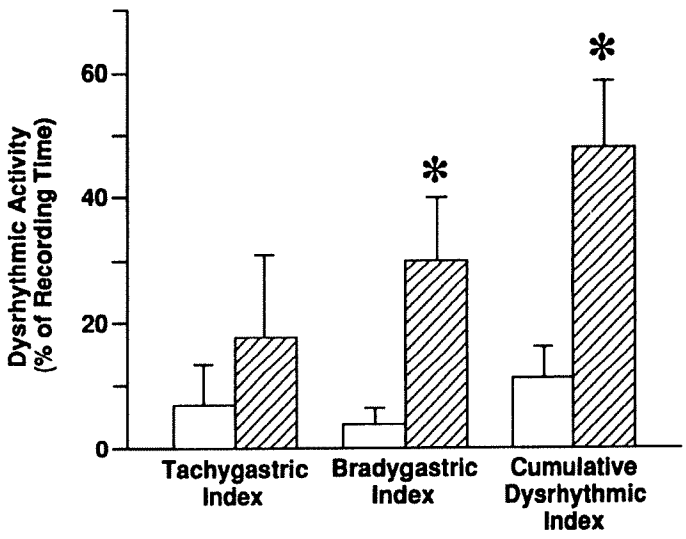

Fig. 6. Dysrhythmic activity in 45-min postprandial period in healthy nonpregnant women before (open bars) and after administration of combination of oral estradiol and progesterone by vaginal suppository (hatched bars). Values are means ± SE (n = 5). There were no significant increases in tachygastric index. *Significant increase in bradygastric ($P < 0.01$) and cumulative dysrhythmic indexes ($P < 0.01$), showing that estrogens potentiate dysrhythmic effects of progesterone.

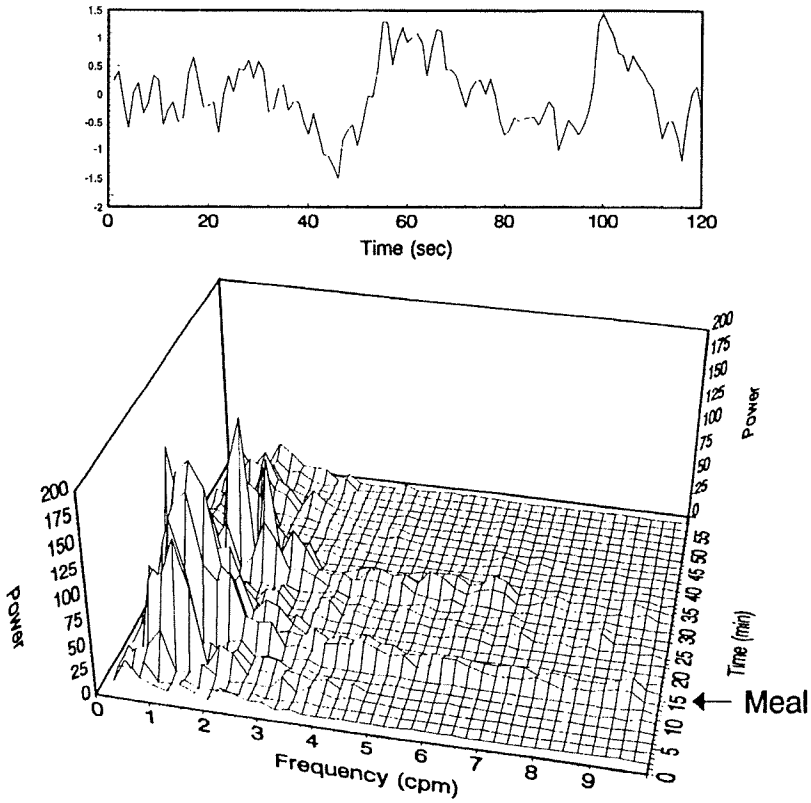

Fig. 7. Sample electrogastrographic results from a healthy nonpregnant woman receiving combination of oral estradiol and progesterone by vaginal suppository. *Top*: raw slow-wave signal showing a slow irregular oscillation with a period of >40 s. *Bottom*: running power spectral analysis of signal showing a predominance of activity in 1- to 2-cpm frequency range throughout study, confirming induction of prolonged bradygastria in this nonpregnant woman with combination of estradiol and progesterone.

present study confirms the observations of Koch and colleagues, demonstrating the presence of gastric dysrhythmias in five of eight pregnant women evaluated. Not all women were symptomatic at the time of study. This may explain why three of the pregnant women exhibited completely normal electrogastrographic recordings. This finding is in agreement with that of Riezzo and colleagues (27), who observed no evidence of tachygastria or bradygastria in asymptomatic women in the first trimester of pregnancy.

The circulating mediators that induce gastric slow-wave dysrhythmias in pregnant women with nausea in the first trimester are unknown. A number of hormones produced by the ovaries and fetal-placental unit increase markedly during the first 3 mo of gestation. Estradiol increases early in pregnancy, reaches levels greater than during the menses after the 5th wk, and slowly rises throughout the remainder of pregnancy (28). Progesterone also increases early in the first trimester and remains elevated until delivery (17). A subset of individuals placed therapeutically on estrogen and progesterone preparations, alone or in combination, developed nausea, suggesting a possible role for these compounds during early pregnancy in the induction of symptoms (11). Furthermore 91% of women who develop nausea on oral contraceptives will subsequently experience nausea during pregnancy, suggesting a possible common etiology (15, 16). Although estradiol and progesterone levels remain elevated until full term, symptoms of nausea on oral contraceptives are most severe in the first 2 mo of therapy, indicating that abrupt increases in circulating hormone levels, rather than absolutely elevated levels, may be responsible for symptoms (12). However, there are no documented differences in circulating estradiol and progesterone levels in nauseated and nonnauseated women in early pregnancy, suggesting that other factors clearly are important.

The present study demonstrates a slow-wave dysrhythmic effect for progesterone that mimics the abnormalities observed in early pregnancy, both qualitatively and quantitatively. By itself, estradiol has no effect on slow-wave rhythmicity, but, given the small number of women evaluated in this study, it is certainly possible that a type II error could have occurred. With the variability of the data obtained, to achieve statistical significance with a power of 80%, >20 women would have been needed to detect a dysrhythmic effect of estradiol. However, the coadministration of estradiol with progesterone significantly potentiates the dysrhythmic effects of progesterone alone. Thus, although progesterone clearly produces slow-wave disruption, these findings suggest that no single mediator may be responsible for the gastric pacemaker disturbances observed in early pregnancy; rather, a complex interaction of elevated circulating hormones may underlie the development of tachygastria and bradygastria in the first trimester. The prevalence of dysrhythmias and nausea during the first trimester, with significant decreases in the second and third trimesters, despite continued elevations in estrogen and progesterone, suggests possible roles for other mediators as well. Alternatively, there may be a desensitization phenomenon with chronically elevated levels of estrogen and progesterone that reduce their dysrhythmic effects

with time. This possibility is worthy of future investigation.

Estrogen and progesterone are only two of many hormones that increase during pregnancy; thus other circulating hormones may be involved in the pathogenesis of gastric dysrhythmias in pregnancy. Levels of β-human chorionic gonadotropin (hCG) increase exponentially to >100,000 mIU/ml in the 6th–12th gestational week only to fall to levels <10% of this peak during the second and third trimesters (3, 9). The role of elevated β-hCG as a cause of the nausea of pregnancy is controversial, inasmuch as different studies have reported higher, lower, or similar β-hCG levels in nauseated and nonnauseated pregnant women (5, 7, 18, 25, 28). Additionally, clinical conditions with elevated β-hCG do not permit a clear identification of an emetogenic role for the hormone. Patients with hydatidiform mole experience significant nausea, whereas those with choriocarcinoma rarely become nauseated, yet each condition is associated with markedly elevated β-hCG concentrations (6, 12). Ideally the effects of β-hCG on gastric slow-wave rhythmicity should have been tested in the present study, which would have provided important information concerning the dysrhythmic effects of this pivotal mediator. However, the commercially available β-hCG preparations that are used in the treatment of infertility do not permit dosing to levels close to those observed in the first trimester of pregnancy. Other hormones increase during pregnancy, including human placental lactogen, prolactin, and free thyroxine, whereas the gastrointestinal hormone motilin decreases (1, 4, 26, 31). Furthermore release patterns of cortisol, adrenocorticotropic hormone, and growth hormone in patients with hyperemesis gravidarum are different from those in asymptomatic pregnant women (13, 14, 19). Nonetheless no clear causal association has been made with any of these hormones and either the nausea of the first trimester of pregnancy or the associated gastric slow-wave dysrhythmias.

The relative distribution of tachygastric and bradygastric activity in the present study also suggests the possible presence of mediators in addition to progesterone and estrogens. Koch and colleagues (24) observed tachygastria in nearly two-thirds of their pregnant patients with gastric dysrhythmias. In the pregnant women evaluated in the current study, there was a statistically significant increase in the CDI, which was composed of nearly equal increases in tachygastric and bradygastric signal activity. However, when hormones were administered to healthy nonpregnant women, a predominance of bradygastric activity was noted, especially with the combination of oral estradiol and progesterone per vaginal suppository. It is possible that the acute administration of these agents results in slowing of the gastric slow wave, whereas chronic elevations during pregnancy might have a more accelerating effect. However, an equally plausible explanation is that other circulating mediators in addition to estradiol and progesterone may be involved in disruption of slow-wave rhythmicity. This issue is worthy of further study.

In conclusion, women with nausea in the first trimester of pregnancy exhibit an increased prevalence of gastric slow-wave dysrhythmias compared with healthy women who are not pregnant. Similar dysrhythmias are induced in healthy nonpregnant women by administration of progesterone alone or in combination with estradiol in doses that reproduce plasma levels in early pregnancy. These data suggest that gastric slow-wave dysrhythmias in pregnancy may result from the combination of elevated levels of endogenous estrogens and progesterone.

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