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Relation of endometriosis and neuromuscular disease of the gastrointestinal tract: new insights

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Objective: To investigate the neuromuscular activity of the gastrointestinal tract by antroduodenal manometry in women with endometriosis documented by laparoscopy, to assess the effects of diet and drug therapy on symptoms, and to assess the bacterial overgrowth that is commonly associated with these nerve diseases.

Design: Prospective, open-label study.

Setting: A clinical center for the care of women's health.

Patient(s): Fifty women with endometriosis documented by laparoscopy and gastrointestinal tract symptoms characterized by chronic abdominal pain, nausea, vomiting, early satiety, bloating and distention, and altered bowel habits.

Intervention(s): Motility of the gastrointestinal tract was recorded and bacterial overgrowth was assessed. Treatment consisted of dietary changes, including reduction of glycemic carbohydrates, balancing with omega 9 oils, elimination of foods with caffeine and tyramine, and addition of omega 3 fatty acids, as well as drug therapy with clonazepam (0.25 mg 3 times per day).

Result(s): All 50 women showed a characteristic motility change (ampulla of Vater–duodenal wall spasm, a seizure equivalent of the enteric nervous system). Forty of the women showed bacterial overgrowth. There was a significant reduction in the total symptom score after 8 weeks of treatment.

Conclusion(s): This study suggests that endometriosis and gastrointestinal tract symptoms are a result of the dysfunction of hollow organs. Correction of the biochemical imbalance of the eicosanoid system and the hypersecretion of insulin that results from excessive intake of glycemic carbohydrates and lack of essential fatty acids significantly decreases symptoms in patients with endometriosis and associated neuromuscular disease of the gastrointestinal tract. (Fertil Steril® 1998;70: 81–8. ©1998 by American Society for Reproductive Medicine.)

Key Words: Prostaglandins, insulin, functional bowel disease, omega fatty acids

Endometriosis is a complex and poorly understood gynecologic and medical illness of significant clinical importance. Medical textbooks describe endometriosis as a benign illness, and yet for many women, this disease results in significant and debilitating symptoms of moderate to severe dysmenorrhea, chronic pelvic pain, and infertility and requires multiple surgical procedures, often leading to total abdominal hysterectomy and bilateral salpingo-oophorectomy (1).

Endometriosis often is associated with debilitating gastrointestinal symptoms of epigastric pain, nausea, vomiting, early satiety, bloating and distention, and altered bowel habits that are worsened by eating and are not relieved by a bowel movement (2). These gastrointestinal symptoms often are classified, inappropriately, as the irritable bowel syndrome. The irritable bowel syndrome has been clearly defined by a working group of gastroenterologists (the Rome criteria) as intermittent or continuous abdominal pain of 3 months' duration that is relieved by a bowel movement and may or may not be associated with altered bowel habits (3). Most patients with endometriosis have symptoms that are worsened by eating and are not relieved by a bowel movement. Defecation often is associated with pain.

The gastrointestinal symptoms of patients with endometriosis classically are expressed at 2 specific times in the menstrual cycle (4). The first is at ovulation, a time when 17-hydroxyprogesterone and subsequently progesterone are secreted, and the second is just before and during menses, a time when progesterone

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and estradiol levels fall and the eicosanoid system is enhanced (4, 5). These periods of recurring and enhanced symptoms account for an emerging area of interest defined as cyclic vomiting (6).

The pathophysiology of endometriosis remains controversial. The most common theory is one proposed by Sampson in 1927 (7). He suggested that endometrial implants result from retrograde flow of endometrial tissue through the fallopian tubes (7). Although this theory does not explain endometrial implants found in nonmüllerian duct tissue, such as lung, skin, and nerve tissue, an understanding of the biochemistry and physiology of the disease may help explain why endometriosis can occur locally or in distant organ systems and result in systemic disease.

We previously have described several neuromuscular diseases of the gastrointestinal tract that occur predominantly in women (ratio of women to men = 20:1) (8). One of these disorders, ampulla of Vater–duodenal wall spasm, represents a loss of inhibitory control and changes in pacemaker rhythm of the bowel (9). This altered motor activity is a "seizure equivalent" of the enteric nervous system (9). The enteric nervous system is responsible for neural control of the hollow viscera (i.e., the gastrointestinal, biliary, urinary, and reproductive tracts). Dysfunction of the enteric nervous system often is found in all or some of the hollow organs and is termed "hollow visceral neuropathy" (8, 10–14).

The purpose of this study was to investigate the motility of the gastrointestinal tract with the use of antroduodenal manometry in women with known moderate to severe endometriosis documented by laparoscopy (15), to assess for the presence of bacterial overgrowth by hydrogen breath testing (14), to assess the effect of restricting glycemic carbohydrates (stimulators of insulin secretion) and foods that contain caffeine and tyramine (excitable transmitters) on gastrointestinal and reproductive tract symptoms, to assess the effect of supplementation with omega fatty acids (to balance the eicosanoid system) on symptoms, and to assess the effect of stabilizing neuroexcitation of the enteric nervous system with the use of clonazepam, a γ-aminobutyric acid agonist ($GABA_A$-agonist).

MATERIALS AND METHODS

Patients

Fifty consecutively seen women who were referred to our clinic for unexplained chronic abdominal pain (epigastric to right upper quadrant), nausea, vomiting, early satiety, abdominal distention, altered bowel habits, or a combination of these symptoms between June 1, 1996 and June 30, 1997 were assessed. Each patient was evaluated extensively by gynecologic testing, including laparoscopy with laser therapy for endometriosis. All the standard tests, including roentgenographic studies (upper gastrointestinal series and barium enema) and endoscopy (esophagogastroduodenoscopy and colonoscopy), had failed to disclose a cause for the gastrointestinal symptoms.

Recording Protocol and Equipment

As part of our routine evaluation for motility disease, the patients underwent a 15-hour recording of the stomach and upper small intestine (antroduodenal manometry). Our protocol for recording involved overnight admission to the hospital for observation. Informed consent was obtained before the study was performed. The subject arrived for the test having fasted for approximately 15 hours. At approximately 3:00 P.M., 4% lidocaine was administered into the nasopharynx. When appropriate anesthesia had been achieved, the probe was passed through the nose and into the stomach.

Under the guidance of a mobile x-ray image intensifier unit (OEC Medical Systems, Inc., Salt Lake City, UT), the tip of the probe was advanced through the pylorus, down the duodenum, and to or just beyond the ligament of Treitz. Thus, the most proximal sensors usually lay in the body and antrum of the stomach, respectively, and the most distal sensors lay in the duodenum, with the fourth transducer located near the ampulla of Vater and the distal transducer located at the duodenal-jejunal junction.

Placement of the probe required about 1 hour. A 12-hour recording of the fasting state began at 5:00 P.M. and continued through the night, when light and noise levels were minimal. The patient usually slept through most of the test. At 5:00 A.M., the subject was awakened and given 237 mL (8 oz) of apple juice to drink; recording continued until 8:00 A.M. to assess conversion to the fed state. The probe then was removed and the patient was given breakfast.

The Millar recording probe has been described in detail previously (15). The recorder (Narco Bio-Systems MMS-200) was interfaced with a computer that stored the motility data on its hard disk for later detailed analysis and simultaneously produced a tracing on high-quality thermal paper. The paper speed was set at 0.5 mm/s and the pressure sensitivity was 20 mm Hg/cm. The 15-hour recording also could be transferred to a floppy disk for storage.

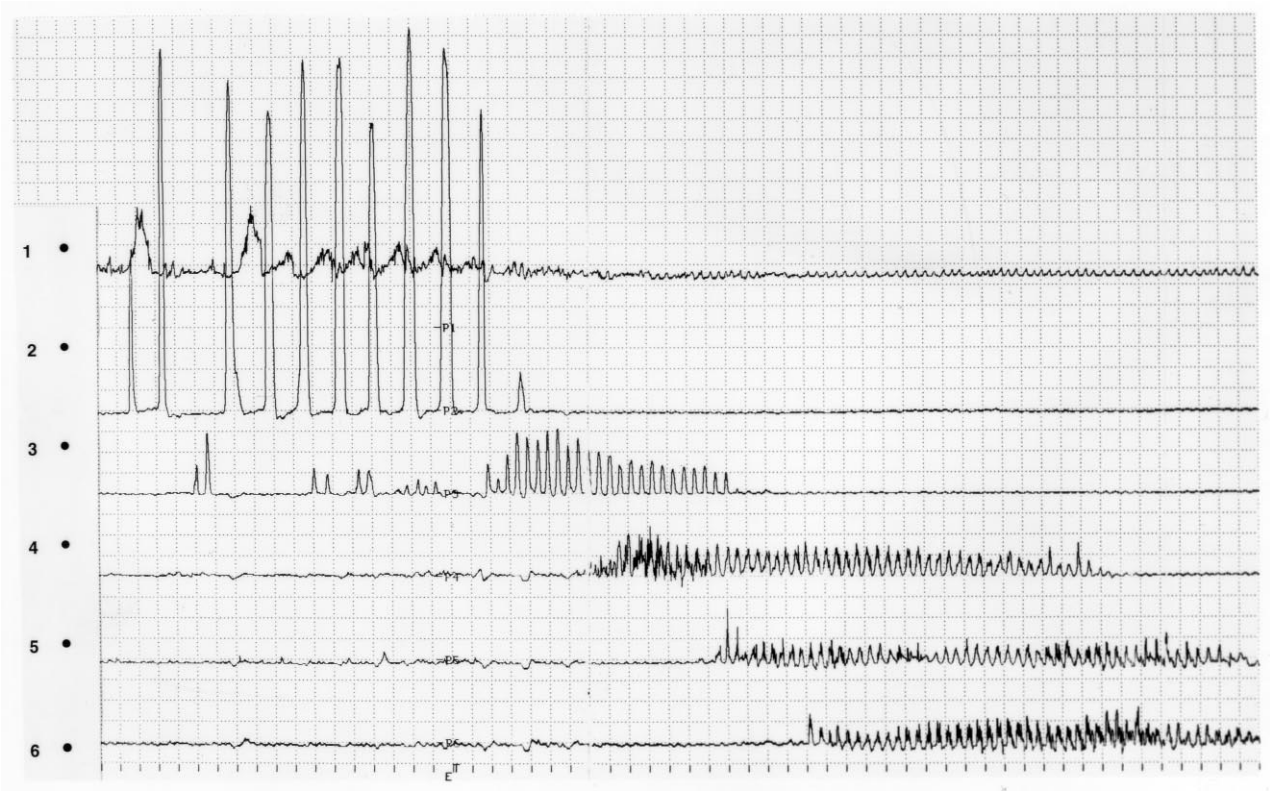
Hydrogen Breath Testing

The hydrogen breath test was performed using a Quintron Microlyzer (Quintron, Milwaukee, WI). The patient was asked to take a breath and then exhale into a small sample bag for a baseline excreted hydrogen sample. Similar samples were taken every 15 minutes for 3 hours after the administration of 10 g of lactulose by mouth (14).

Oral-to-cecal transit time was evaluated as the time required for an increase in the breath hydrogen value of >20 parts per million (ppm) to occur. Bacterial overgrowth was defined as either an increased baseline breath hydrogen value of >20 ppm or a rise and fall in the breath hydrogen value consisting of at least 3 separate peaks of >20 ppm over the 3-hour test period (14).

FIGURE 1

A representative example of phase III of the migrating motor complex from a healthy control subject without endometriosis. Transducer leads 1–6 are indicated (*left*). Leads 1 and 2 are located in the body and antrum of the stomach, respectively; lead 3 is in the first part of the duodenum; lead 4 is in the second part of the duodenum near the ampulla of Vater; lead 5 is in the third part of the duodenum; and lead 6 is at the duodenal-jejunal junction. The propagation of this complex is 3.5 cm/min, and the amplitude of contractions is within the normal range of 40–60 mm Hg. Each square represents 20 mm Hg. The time is shown at the bottom of the tracing, and each tic equals 10 seconds.



This study was approved by the institutional review board of Woman's Hospital of Texas, (Houston, Texas).

Data Analysis

We assessed the prevalence of gastrointestinal tract motility events in the 50 consecutively seen patients with endometriosis documented by laparoscopy who also had gastrointestinal complaints. Ampulla of Vater–duodenal wall spasm was analyzed for onset from the beginning of the recording period, the duration of the spasm periods, and recognizable variations. Symptom scores were analyzed using the Mann-Whitney *U* test, and $P<0.05$ was considered statistically significant.

RESULTS

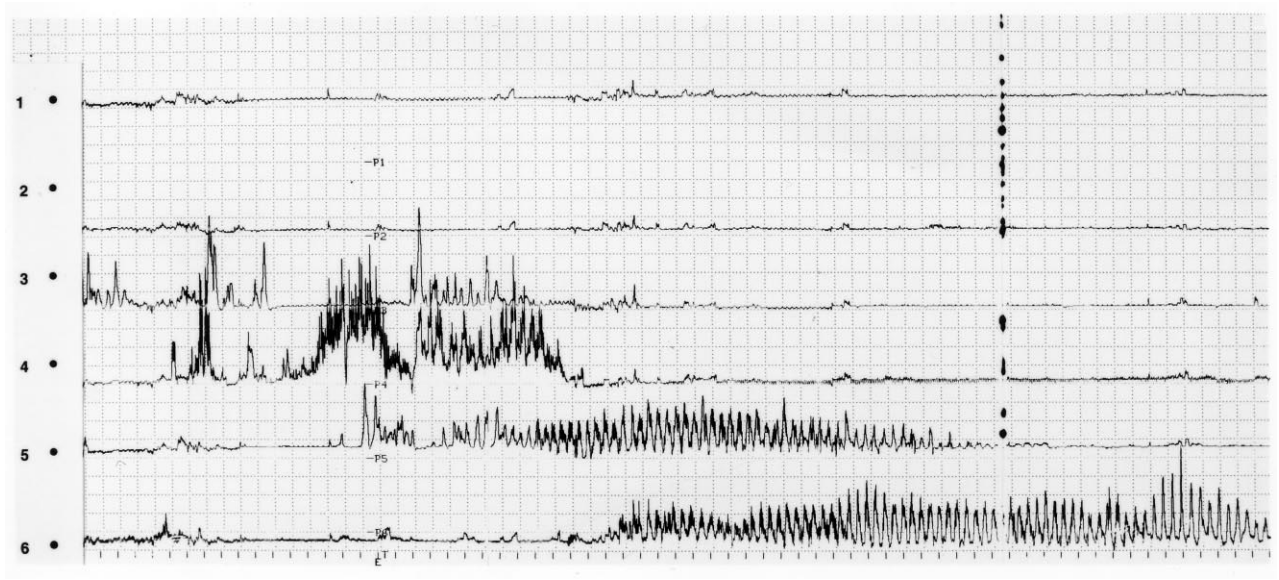
Fifty consecutively seen women with endometriosis documented by laparoscopy who were referred for intractable gastrointestinal symptoms were investigated. All patients had unexplained gastrointestinal tract symptoms refractory to standard therapy. Their mean (±SD) age was 34 ± 4.5 years. All patients either were of northern European ancestral background or had northern European ancestral genetic crossing (i.e., Native American or Hispanic).

All 50 patients had ampulla of Vater–duodenal wall spasm. The mean onset time for the spasm was 4.5 hours after the recording began, and it usually was most active between 11:00 P.M. and 3:00 A.M. Most episodes were independent of the biorhythm of the gastrointestinal tract (i.e., the migrating motor complex).

Figure 1 shows an example of phase III of the migrating motor complex in a control subject without endometriosis. Normal contractions at a rate of 3 per minute were seen in the body and antrum of the stomach (leads 1 and 2), respectively, and normal contractions at a rate of 11 per minute were seen in the duodenum (leads 3–5) and upper jejunum (lead 6). The propagation velocity of the migrating motor complex was 3.5 cm/min and its integrity was organized. The mean (±SD) amplitude of contractions in the small

FIGURE 2

A representative example of ampulla of Vater–duodenal wall spasm associated with phase III of the migrating motor complex from a subject with endometriosis. Transducer leads 1–6 are indicated (*left*). Leads 1 and 2 are located in the body and antrum of the stomach, respectively; lead 3 is in the first part of the duodenum; lead 4 is in the second part of the duodenum near the ampulla of Vater; lead 5 is in the third part of the duodenum; and lead 6 is at the duodenal-jejunal junction. An episode of ampulla of Vater–duodenal wall spasm is shown on lead 4, with phasic activity at 44 cycles per minute superimposed on an increase in baseline pressure approaching 100 mm Hg. The normal amplitude of contractions (nonspasms) is within the normal range of 40–60 mm Hg. Each square represents 20 mm Hg. The time is shown at the bottom of the tracing, and each tic equals 10 seconds.



intestine was between 40 and 60 mm Hg (normal amplitude = 40–60 mm Hg). There was no deviation of the phasic contractions from baseline on any lead.

Figure 2 shows an example of spontaneous ampulla of Vater–duodenal wall spasm associated with phase III of the migrating motor complex on lead 4 located in the second part of the duodenum near the ampulla of Vater in a patient with endometriosis. The baseline tone associated with these spasms increased in amplitude to approximately 100 mm Hg and they were associated with phasic contractions at a rate of 44 per minute. This activity is a seizure equivalent of the enteric nervous system (9).

Figure 3 shows an example of ampulla of Vater–duodenal wall spasm just after the migrating motor complex on lead 5 located in the second part of the duodenum near the ampulla of Vater in a patient with endometriosis. Again, there was an increase in the baseline pressure to approximately 80 mm Hg and phasic contractions at a rate of 44 per minute were seen superimposed on the increase in baseline pressure.

Figure 4 shows an ampulla of Vater–duodenal wall spasm occurring independent of the migrating motor complex on lead 4. This is the most common expression of this abnormality and this type of activity usually occurs at night, beginning at approximately 11:00 P.M. and lasting until 3:00 A.M. This type of activity often is elicited by giving the patient apple juice to induce the fed state. This type of activity may occur intermittently or in prolonged episodes lasting from minutes to hours.

Hydrogen Breath Testing

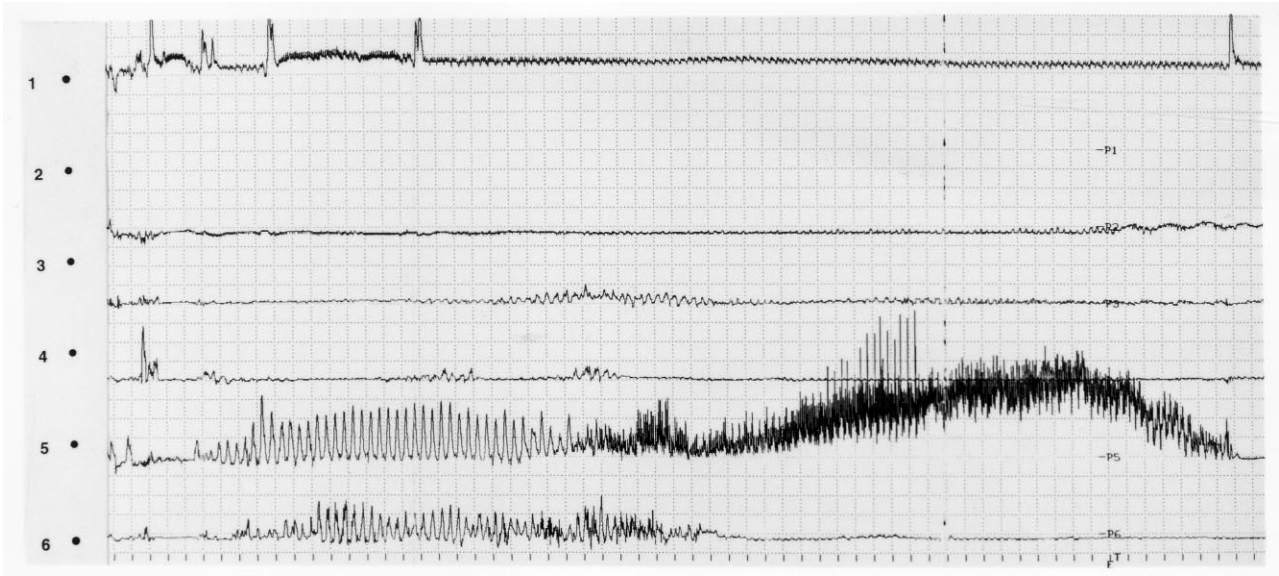
Forty of the 50 patients were shown to have bacterial overgrowth after lactulose was administered and the excretion of breath hydrogen was measured (14). The other 10 patients had a markedly delayed oral-to-cecal transit time, suggesting impaired motility (16).

Dietary Changes

All patients were instructed to omit foods that contained significant amounts of caffeine and tyramine (Table 1), both of which are excitatory transmitters that stimulate nerves within the central nervous system and the enteric nervous system. In addition, omega 3 fatty acid from flax seed (Barlean's Organic Oils, Ferndale, WA) was administered to all patients to balance the eicosanoid system (Table 2). The starting dose was 1 capsule by mouth 3 times per day. Each patient also was instructed to reduce or eliminate glycemic carbohydrates (the stimulus for insulin secretion) from their food intake (Table 3).

FIGURE 3

A representative example of ampulla of Vater–duodenal wall spasm expressed at the end of phase III of the migrating motor complex from a subject with endometriosis. Transducer leads 1–6 are indicated (*left*). Leads 1 and 2 are located in the body and antrum of the stomach, respectively; lead 3 is in the first part of the duodenum; lead 4 is in the second part of the duodenum near the ampulla of Vater; lead 5 is in the third part of the duodenum; and lead 6 is at the duodenal-jejunal junction. An episode of ampulla of Vater–duodenal wall spasm is shown on lead 5, with phasic activity at 44 cycles per minute superimposed on an increase in baseline pressure approaching 80 mm Hg. The normal amplitude of contractions (nonspasms) is within the normal range of 40–60 mm Hg. Each square represents 20 mm Hg. The time is shown at the bottom of the tracing, and each tic equals 10 seconds.



$GABA_A$ Agonist Therapy

All patients were treated with clonazepam, 0.25 mg orally 3 times per day. This $GABA_A$-agonist was used to stabilize the seizure activity of the enteric nerves (ampulla of Vater–duodenal wall spasm) (17). All patients graded their gastrointestinal tract symptoms on a scale of 0 (no symptoms) to 10 (worst symptoms) before the initiation of dietary changes and clonazepam therapy. After 8 weeks of treatment, the mean ($\pm$SD) symptom score was 2.8 ± 2.3. This difference was statistically significant compared with baseline values ($P<0.001$). This clinical response resulted from the combination of dietary and pharmacologic therapies working together.

DISCUSSION

We have shown a consistent and distinct abnormality of bowel function in women with endometriosis. This abnormal motility pattern, ampulla of Vater–duodenal wall spasm, is a result of injury to or a lack of inhibitory control of the enteric nervous system (9). The inhibitory neural circuits are the nonadrenergic, noncholinergic inhibitory system, the neural transmitter is nitric oxide and/or the postganglionic adrenergic neurons from the spinal cord, and the neural transmitter is norepinephrine-epinephrine.

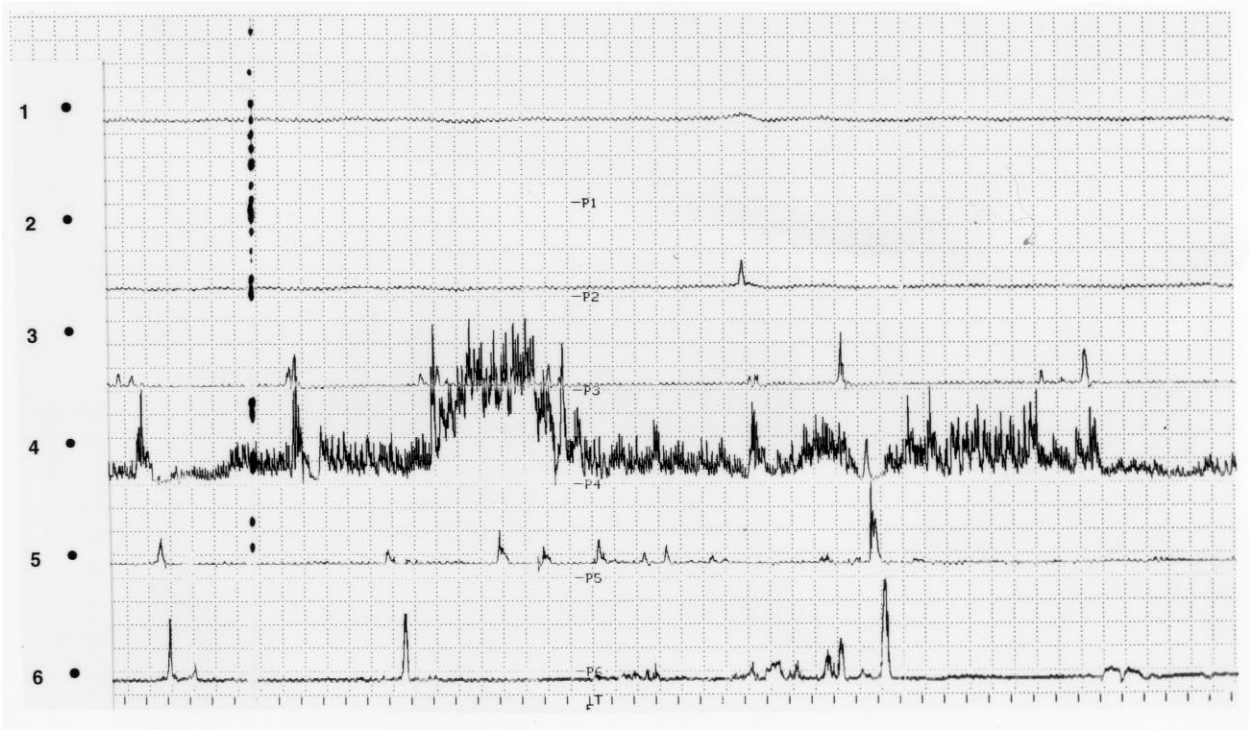
The enteric nervous system expresses a biorhythm called the migrating motor complex. In primates, the migrating motor complex occurs only in the fasted state and cycles the intestine approximately every 80–90 minutes (18). The migrating motor complex is replaced by the "fed state" (a series of random contractions in the bowel) when nutrients are present in the intestine. Once the nutrients have passed or have been absorbed, the migrating motor complex recurs. The migrating motor complex occurs in other mammals and in birds (warm-blooded vertebrates) in both the fasted and fed states (19–21), suggesting that this complex may have been involved in the digestive processes of earlier life forms.

The function of the migrating motor complex in humans remains unclear. The migrating motor complex is an ancient biorhythm and is unique to the gut-brain (i.e., the enteric nervous system). The clinical importance of the migrating motor complex lies in the fact that normal nerve and circular smooth muscle function must be present for the expression of this cycling event. Therefore, recording the motility of the gastrointestinal tract, including the migrating motor complex, has become a useful diagnostic tool in assessing the integrity of the enteric nervous system (8, 15).

The fallopian tube is a hollow organ whose function is to transport the ovum from the ovary to the uterus. Neuromus-

FIGURE 4

A representative example of ampulla of Vater–duodenal wall spasm independent of the migrating motor complex. Transducer leads 1–6 are indicated (*left*). Leads 1 and 2 are located in the body and antrum of the stomach, respectively; lead 3 is in the first part of the duodenum; lead 4 is in the second part of the duodenum near the ampulla of Vater; lead 5 is in the third part of the duodenum; and lead 6 is at the duodenal-jejunal junction. An episode of ampulla of Vater–duodenal wall spasm is shown on lead 4, with phasic activity at 44 cycles per minute superimposed on an increase in baseline pressure approaching 100 mm Hg. The normal amplitude of contractions (nonspasms) is within the normal range of 40–60 mm Hg. Each square represents 20 mm Hg. The time is shown at the bottom of the tracing, and each tic equals 10 seconds.



cular control of the fallopian tube most likely involves the enteric nervous system. If the fallopian tube is dysfunctional in a manner similar to that of the gastrointestinal tract, then Sampson's (7) hypothesis of retrograde implantation is clearly plausible; we strongly support the concept of retrograde implantation based on a dysfunctional enteric nervous system. If we accept the concept that endometrial implants occur because of retrograde flow, then the key question is what is the underlying hormonal/biochemical abnormality? We suggest that this abnormality is the hypersecretion of insulin and we offer the following explanation.

The range of insulin is the most diverse of any hormone in our body (22). When hypersecretion of insulin occurs, it results in an imbalance at both the cellular and intracellular levels. From a practical standpoint, the control of insulin depends on a proper diet that includes certain nutrients that allow our body to function properly (23).

One of the important intermediate functions that insulin controls is the eicosanoid system, perhaps the most important regulatory system in our body (23, 24). The eicosanoid system is maximally stimulated just before and during menses, a time when retrograde implantation of endometrial tissue is most likely to occur. Just before menses, estradiol and progesterone levels fall, and it has been suggested that hypersecretion of insulin occurs, resulting in the production of 2 pathway prostaglandins (PGE_2 and $PGF_{2\alpha}$). These 2 pathway prostaglandins can be measured in high concentrations in peritoneal explants (25, 26) before and during menses.

We also have shown previously that when PGE_2 is placed into the lumen of the intestine, it results in an electrical complex (repetitive bursts of action potentials) that causes a nonpropulsive mechanical event (seizure activity) (27). This same process also may occur in the fallopian tube, resulting in spasm or retrograde flow of uterine tissue.

The key to regulating the production of the favorable versus the unfavorable prostaglandins is to control insulin. Insulin is the control mechanism that determines whether pathway 1 or pathway 2 prostaglandins are produced (23). We teach our patients to decrease or eliminate glycemic carbohydrates from their diet and to begin using the oils that are so important: omega 3 fatty acids (eicosapentanoic acid

TABLE 1

Caffeine- and tyramine-containing foods.

Caffeine
Coffee, tea, colas, decaffeinated colas, chocolate milk
Tyramine
Aged Cheeses
Brick, blue, cheddar, Camembert, Swiss, Romano, Roquefort, Stilton, mozzarella, parmesan, provolone, Emmentaler, Boursin, Brie, sour cream, yogurt
Beverages
Ale, sherry, brandy, liqueurs, liquor (e.g., Scotch, bourbon), red wine, coffee, tea, hot chocolate, cola drinks
Meats
All red meat (e.g., beef, pork, lamb, goat), canned meats, fermented sausage or salami, pepperoni, summer sausage, bologna
Fish
Salted or pickled herring, dried fish, caviar
Vegetables
Flat beans, Chinese pea pods, fava beans, mixed Chinese vegetables
Fruit
Figs, avocados, bananas
Miscellaneous
Chocolate, soy sauce and soy extracts

or alpha-linolenic acid), omega 6 fatty acid (gamma-linolenic acid), and the governor of insulin, omega 9 fatty acid (oleic acid) (Table 2). It is important to remember that we are genetically programmed to digest green vegetation, fruits and berries, and foods that contain the omega oils (i.e., nuts and fish).

Humans never were genetically programmed to consume large amounts of glycemic carbohydrates that result in the hypersecretion of insulin and cellular imbalance. Our nervous system has not taken kindly to this change in essential nutrients. We are biochemically out of balance because our dietary habits do not fit our genetic programming.

Ampulla of Vater–duodenal wall spasm represents seizure activity of the enteric nervous system (9). The elimination of foods that contain caffeine and the amino acid tyramine (a stimulatory amino acid) from the diet further decreases the excitatory activity of the enteric nervous system (Table 1) and decreases symptoms of the gastrointestinal tract. Nemeth et al. (28) showed that cholecystokinin causes hyperexcitability of Dogiel type III neurons of the myenteric plexus in strips of duodenum near the ampulla of Vater. Thus, cholecystokinin not only functions as a hormone that results in the secretion of bile and the contraction of the gallbladder but also may exhibit neurotransmitter effects on enteric neurons.

TABLE 2

Dietary sources of omega fatty acids.

Omega fatty acid	Dietary source
Omega 9 (oleic acid)	Olive oil (olives), canola oil, peanut oil (peanuts), nuts
Omega 6 (linoleic acid)	Corn oil, safflower oil, sunflower oil
Omega 3	Nutritional supplements
Eicosapentanoic acid	
Alpha-linolenic acid	
Docosahexanoic acid	

TABLE 3

Glycemic carbohydrates.

Rice
Potatoes
Gluten-rich bread
Pasta
Carrots
Corn
Beets
Peas and flat beans
Fruit juices

This helps explain the findings shown in Figures 2 and 3, where the phasic activity at a rate of 44 per minute is superimposed on an elevation of the baseline pressures during the expression of the migrating motor complex. Cholecystokinin is released during the expression of phase III of the migrating motor complex and results in bile flow (29). The activity seen in Figure 4, however, is most likely the effect of other agonists, such as growth hormone or the transmitters released from stimulation by corticotropin-releasing factor, on damaged enteric neurons (unpublished data).

In addition, the use of $GABA_A$-agonist to reduce the seizure activity further enhances the control of this disease. γ-Aminobutyric acid receptors are numerous in the nerves of the enteric nervous system (30–34). γ-Aminobutyric acid is the main inhibitory transmitter of neural excitability in the enteric nervous system and certain centers in the central nervous system, such as the limbus and the temporal lobes. The use of $GABA_A$-agonist is important in controlling this seizure activity of the enteric nervous system and further stabilizing neural excitation. Two prospective, placebo-controlled studies, one by Smith et al. (35) and one by Harrison et al. (36), have shown a significant reduction in symptoms with the use of alprazolam in women with premenstrual syndrome.

In summary, we have shown that a characteristic dysfunction of the enteric nervous system exists in the bowel of patients with endometriosis. This same neuromuscular dysfunction most likely exists in the fallopian tubes (hollow viscera). The visible objective expression of this dysfunction is endometrial implants detected by laparoscopy and ampulla of Vater–duodenal wall spasm in the intestine detected by

recording technology. The biochemical abnormality appears to be the hypersecretion of insulin, resulting in the production of excessive pathway 2 prostaglandins that cause seizure activity of the enteric nerves.

Omitting foods that are neural stimulants (caffeine and tyramine), reducing glycemic carbohydrates (the stimulus for insulin release), supplementing with omega 3 (the precursor of pathway 3 prostaglandins) and omega 9 (the governor of insulin release) fatty acids, and providing neural stability with a $GABA_A$-agonist results in control of the disabling symptoms of this common disease involving the hollow viscera.

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