Gastroparesis in pregnancy: case report and literature review

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Summary: Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction. The most common underlying aetiology is diabetes mellitus; however, many cases are idiopathic. Pregnancy *per se* is associated with gastrointestinal neuromuscular dysfunction; however, reports of gastroparesis arising during pregnancy are rare. We report a case of severe gastroparesis and proximal small bowel paresis presenting during pregnancy.

Keywords: gastroenterology, high-risk pregnancy

CASE REPORT

A 24-year-old primigravida, at 10 weeks gestation, presented with nausea, vomiting, colicky right lower quadrant pain and an elevated white cell count. There was no history of fevers. She underwent uncomplicated laparoscopic appendectomy; however, she was found to have congenital malrotation of the bowel, and the appendix, located in the right upper quadrant, was normal on histology. No cause of the right lower quadrant pain was identified.

Post appendectomy, the patient had ongoing symptoms and developed intractable large volume vomitus, initially containing 'old' food, and absence of bowel motions with minimal flatus. Two weeks later the patient presented to the emergency department with ongoing symptoms and 7 kg weight loss (8.1% of initial body weight, body mass index 31.6). The vital signs showed a blood pressure of 110/70 (postural drop of 20 mmHg in systolic blood pressure), heart rate 96 beats per minute and temperature 37.1°C. On examination the patient appeared unwell with clinical signs of dehydration and right lower quadrant abdominal tenderness with abdominal distension. There were no clinical features consistent with an autonomic or peripheral neuropathy. Laboratory tests were notable for the presence of a marked electrolyte disturbance, acute renal impairment with an elevated urea/creatinine ratio (in keeping with dehydration) and deranged liver function tests (Table 1). The lipase and lactate were normal.

The patient was prescribed antiemetic medication (metoclopramide, prochlorperazine and ondansetron), vitamin supplementation (thiamine and multivitamin), intravenous fluid therapy and kept nil by mouth. With hydration there was resolution of the postural drop, normalization of the renal and electrolyte disturbances, and improvement of the liver function tests. There was little change in symptomatology.

An abdominal ultrasound showed a normal gallbladder, pancreas, spleen, kidneys and ureters with diffuse fatty infiltration of the liver (likely secondary to rapid weight loss). On day 8, an upper endoscopy performed showed a dilated stomach with a large amount of fluid residue. No focal abnormality was detected. The first and second parts of the duodenum were grossly dilated with an apparent transition point between segments D2 and D3 with no mucosal abnormality visualized. The distal D3 segment appeared normal. Gastric mucosal biopsy was normal. A diagnostic laparoscopy on day 9 revealed a dilated stomach with inflammatory adhesions at the duodenum, thought to be a point of obstruction. Adhesiolysis was performed. A nasogastric tube was inserted with aspiration of large volume fluids. There was no change in the patient's symptoms postadhesiolysis. On day 11 a nasojejunal tube (NJT) was inserted for enteral feeding. At insertion, there was a large amount of bile present in the stomach and the dilated D1–D2 segment persisted. Parenteral nutrition was commenced on day 12. Limited magnetic resonance imaging (MRI) of the abdomen on day 13 confirmed malrotation visualizing the duodenum and entire small bowel on the right side of the midline and large bowel on the left. The stomach and proximal duodenum were dilated. Below the right upper quadrant, the proximal small bowel was collapsed (see Figure 1). A repeat gastroscopy confirmed previous findings. A laparotomy was performed on day 23 and showed no band or adhesions obstructing the duodenum. Gastrojejunostomy was also performed and a jejunal feeding tube was inserted. The patient was able to tolerate small volumes of oral liquids on day 28 of admission. Within 24 hours of commencement of oral intake, the patient had recurrent nausea with large volume vomitus (up to 1.5–2 L). A plain abdominal film postoral gastrograffin showed contrast in the stomach and proximal small bowel. The proximal small bowel was dilated (see Figure 2). A repeat gastroscopy showed a large residue of fluid and food in stomach. The gastrojejunostomy was widely patent. Complete absence of peristalsis movements in the small bowel limbs and stomach was noted. A diagnosis of gastroparesis and small bowel paresis was made. Erythromycin and domperidone were commenced with no benefit. Mirtazepine was trialled with no significant improvement.

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Table 1 Biochemical and hematinic results on admission

Sodium	129 mmol/L
Potassium	2.9 mmol/L
Chloride	81 mmol/L
Bicarbonate	30 mmol/L
Corrected calcium	2.59 mmol/L
Phosphate	1.66 mmol/L
Creatinine	125 μ mol/L
Urea	36 μ mol/L
Urate	0.87 mmol/L
Albumin	34 g/L
Conjugated bilirubin	9 μ mol/L
Alkaline phosphatase	102 U/L
Gamma-GT	102 U/L
Alanine transaminase	245 U/L
Aspartate transaminase	109 U/L
Lactate dehydrogenase	248 U/L
Haemoglobin	124 g/L
White cell count	17.2×10^9 /L
Neutrophils	11.28×10^9 /L
Lymphocytes	4.43×10^9 /L
Monocytes	1.09×10^9 /L
Platelet	360×10^9 /L
Free T4	19 pmol/L
Thyroid-stimulating hormone	0.6 mU/L

The patient had a personal and family (mother) history of systemic lupus erythematosus (SLE) with small joint arthralgias, oral ulceration, photosensitive rash and an antinuclear antibody titre of >2560 (homogeneous pattern). On hydroxychloroquine 400 mg daily, there was improvement in these symptoms. This agent had been ceased prior to pregnancy

Figure 1 Magnetic resonance image of the abdomen

Figure 2 Plain abdominal X-ray of the abdomen post oral contrast

because of the patient's concerns regarding safety during pregnancy but was reinstated on admission after consultation with the obstetric medical unit. There was no prior history of gastrointestinal involvement prepregnancy. During the admission, the patient developed arthralgias but no other features of SLE. Blood tests showed an elevated antinuclear antibody (ANA) titre of 640 (homogeneous pattern) with normal double-stranded DNA (2IU) and negative extractable nuclear antibodies (anti-Ro, anti-La, ribonuclear protein, Smith, Scl70, proliferating cell nuclear antibody, Jo-1 and PM1), normal C3 and C4 levels (1.72 and 0.31 g/L, respectively). Anticentromere antibodies were also negative. The C-reactive protein was mildly elevated (20 mg/L). Lupus anticoagulant and anticardiolipin antibodies were negative and anti β 2 glycoprotein 1 was absent. Anti-Hu and anti-Ri antibodies were uninterpretable due to the presence of an ANA detected during neuronal immunofluorescence testing. The patient was commenced on hydrocortisone 100 mg twice daily, intravenously on day 16, under the guidance of the consulting rheumatology service for possible lupus-related gastrointestinal disease. There was no clinical response; however both prednisolone in a weaning dose and hydroxychloroquine were continued on discharge.

Fetal ultrasound on presentation showed a single live fetus at 11 weeks gestation. A detailed morphology scan at 19 weeks gestation showed no morphological abnormalities and appropriate fetal growth.

Nutritional status, including iron stores, vitamin B₁₂ and folate were within the normal range on supplementation (iron 27 μ mol/L, transferrin 2.4 g/L, transferrin saturation 45%, ferritin 115 μ g/L, vitamin B₁₂ 239 pmol/L, red cell folate 1090 nmol/L), and weight was maintained.

From 30 weeks gestation the patient's symptoms showed progressive improvement allowing cessation of supplemental nutrition at 34 weeks gestation. A liveborn male weighing 2200 g was delivered at 38 weeks gestation via caesarean section for intrauterine growth restriction and anhydramnios. Histological examination of the placenta revealed poor perfusion and ischaemic changes. The patient developed

preeclampsia on day 2 postpartum, which resolved spontaneously enabling discharge on day 5 postpartum.

DISCUSSION

The aetiology of gastroparesis is diverse, with diabetes mellitus implicated in 30% of cases, and in up to 50% of cases no cause is identified. Potential causes include connective tissue diseases, preceding viral infections (including Norwalk virus and rotavirus) and medication side-effects. Disruption of the vagus nerve, lower thoracic spinal sympathetic outflow or myenteric plexus through surgery, neurological disorders or malignancy with direct tumour infiltration or a paraneoplastic syndrome, most commonly due to small cell lung cancer,^{1,2} can also cause gastroparesis.

The pathophysiology of gastroparesis is unknown but multiple mechanisms have been proposed, mostly in the diabetic population. An underlying autonomic neuropathy has been regarded as a contributing factor with animal studies showing reduced autonomic neurons and apoptosis of enteric neurons.³ Loss of the interstitial cells of Cajal (ICC),³ the pace-makers of the intestine, has been observed in up to 30% of cases with severe refractory gastroparesis. Contributory factors to the loss of these cells include disturbances in the nitric oxide regulation, a survival factor for the ICC.⁴ Loss of upregulation of the haeme-oxygenase 1 pathway with resultant increased levels of reactive oxygen species has been shown to influence the development of diabetic gastroparesis.⁵ Further, in diabetic gastroparesis, there is a direct effect of hyperglycaemia on gastric emptying.⁶ In the non-diabetic population, elevation of blood sugar levels is correlated with reduction in gastric contractions and slowed emptying⁶ likely mediated by incretins to control the delivery of nutrients to distal bowel segments. When arising as a result of a paraneoplastic phenomenon, gastroparesis is usually the result of the antineuronal antibodies (anti-Hu) produced by a remote carcinoma.²

The gold standard diagnostic test for gastroparesis is a scintigraphic gastric emptying study with assessment of the gastric residual at four hours.⁷ The radiation dose associated with this procedure precluded its use in our patient. Breath tests for ¹³C-labelled octanoic acid is an alternative test with no radiation exposure but carries a lower sensitivity and specificity (86% and 80%, respectively).⁸ Functional ultrasonography using techniques such as realtime ultrasonography or duplex Doppler also enables visualization of changes in gastric emptying. While this has the advantage of avoiding radiation exposure, it requires a skilled operator and there is limited evidence regarding its use in assessing the emptying of solids which is often first affected in patients with gastroparesis.⁹ Intraluminal pressure with surface electrical profiles and MRI are not used in current practice.

Gastroparesis shows a female predominance, the cause of which is not fully elucidated but has been partly attributed to reduction in gastric contractility from progesterone during the luteal phase¹⁰ and the increased prevalence of autoimmune conditions associated with gastroparesis in women.

The differential diagnosis for this patient includes lupus or scleroderma-related gastrointestinal disease, hyperemesis gravidarum, superior mesenteric artery syndrome and idiopathic gastroparesis exacerbated by pregnancy. Up to 50% of patients with established SLE develop gastrointestinal symptoms during the course of their disease. Soykan *et al.*¹¹ in a study of 146 patients with gastroparesis found the incidence of

connective tissue-related gastroparesis to be 4.1%, including one patient with SLE. Another recognized, but uncommon, manifestation of SLE is chronic intestinal pseudo-obstruction, which presents with signs and symptoms of a bowel obstruction in the absence of an obstructive lesion, and both gastric dysmotility and delayed gastric emptying have been documented.¹² In one series by Mok *et al.*, all six patients had serological abnormalities consistent with an exacerbation of lupus at the time of diagnosis, which was not seen in our patient. Further, a response to high-dose corticosteroids was noted in all six patients and a further 11 of 12 case reports. Other case reports have shown benefit with addition of erythromycin and other promotility agents.¹³ Our patient showed no improvement with these treatments. A possible explanation for the poor response to therapy in this patient was the delay in commencement of immunosuppressants, which resulted in non-resolution of symptoms in a previous case report.¹⁴ In 12 of the 18 patients reviewed by Mok *et al.* and isolated case reports,^{14,15} associated bilateral ureterohydronephrosis and megacholecystitis were noted, which was absent in our patient. The classical histological feature of gastroparesis is intestinal leiomyocyte damage,¹³ thus the normal gastric mucosal biopsy in this patient does not assist with the differential.

Although the patient's presentation is atypical for lupus-related gastrointestinal disease, an underlying mixed connective tissue disorder with scleroderma-associated gastrointestinal involvement is possible. Delayed gastric and small bowel emptying (most commonly affecting the duodenum) have been previously documented in scleroderma, occurring in up to 62.5% and 74% of patients, respectively, in one series.¹⁶ Most cases of scleroderma are associated with cutaneous manifestations, in particular skin induration, which was absent in this patient. Systemic sclerosis sine scleroderma remains a possibility given the absence of cutaneous signs and a previous case report has documented megaduodenum in such a patient.¹⁷ The negative anti-RNP, anti-Scl70 and anti-centromere antibodies do not exclude scleroderma given their poor sensitivity. Therefore, this remains a plausible cause for the patient's presentation.

Hyperemesis gravidarum was thought unlikely given the history of large volume vomitus, absence of bowel motions, imaging studies consistent with bowel obstruction and finding of aperistalsis on endoscopy. The patient's symptoms predated the initial laparoscopy and as such, injury to the vagus nerves was unlikely. Pregnancy *per se* has been associated with gastrointestinal neuromuscular dysfunction.¹⁸ Gastric dysrhythmias, demonstrated in patients with diabetic¹⁹ and idiopathic²⁰ gastroparesis have been documented in pregnancy and their occurrence correlates with nausea during the first trimester.¹⁸ Refractory gastroparesis, however, has not been previously reported.

Superior mesenteric artery syndrome can cause a proximal small bowel obstruction; however, this was excluded by subsequent investigations which failed to show compression of the duodenum between the superior mesenteric artery and aorta.

The imaging studies in this patient are of interest given the recurrent finding of an abrupt transition from dilated to collapsed bowel, which would usually be consistent with a mechanical bowel obstruction. The pathophysiological explanation for the abrupt transition point and finding of aperistalsis in the stomach and proximal small bowel in this patient is unknown.

The management of gastroparesis is multifactorial and includes supportive, pharmacological and interventional therapies. Initial therapy focuses on the correction of electrolyte disturbances, vitamin deficiencies and rehydration. The dietary changes involve the consumption of small volume meals consisting of low fibre, low-fat foods and the avoidance of foods that stimulate gastric emptying (caffeine, tobacco) or reduce lower oesophageal pressure (caffeine, fat, chocolate). Enteral feeding is indicated for severe weight loss of more than 5–10% over 3–6 months, recurrent hospitalization or other significant complications, for example diabetic ketoacidosis or poor quality of life. If oral supplementation is unsuccessful jejunal feeding initially with a NJT and if tolerated a jejunostomy may be indicated. In the absence of a widespread motility disorder parenteral nutrition is usually avoided. It was, however, briefly used in this patient as a bridging treatment prior to the establishment of a definitive route of nutrition.

Medical therapy focuses on prokinetics and antiemetics. The former includes erythromycin, metoclopramide, domperidone and cisapride. Cisapride, due to its association with prolongation of the corrected QT interval and cardiac arrhythmias, has been withdrawn from common usage but remains obtainable under special circumstances. None of these agents was effective in this patient. Cisapride was not used because of safety concerns. A poorer response to prokinetic therapy has been noted in patients with underlying connective tissue disease.¹¹ Botulinum toxin injection into the pylorus has been shown to improve gastric emptying and symptoms; however, no long-term benefits have been demonstrated.²¹ Investigational agents including ghrelin agonists,³² itopride (D2 receptor antagonist and angiotensin-converting enzyme inhibitor³³), tegaserod (5HT₄ receptor agonist²²) and Epalrestat (aldose reductase inhibitor)²³ have shown either conflicting or disappointing clinical results in trials. Other agents shown in animal or human studies to benefit gastric emptying including levosulpiride,²⁴ sildenafil,²⁵ sympathomimetic amines (dextroamphetamine sulphate), mirtazapine²⁶ and clonidine.²⁷ Octreotide has conflicting effects on digestive motility.¹² Tricyclic antidepressants have also been incorporated as a routine therapy and when combined with prokinetic agents, a response rate of 71% has been noted.²⁸

Surgical intervention (other than provision of a gastrostomy or jejunostomy) is usually reserved for patients with gastroparesis postvagotomy and involves completion or subtotal gastrectomy.¹ Regardless of the aetiology, up to one-third of patients showed no improvement on postsurgical intervention.²⁹

Gastric electrical stimulation delivering high-frequency/low-energy stimulation via an implantable device has been employed in patients with refractory symptoms with benefits seen on symptomatology, body weight, requirements for medications and supplemental nutrition and quality of life.^{30,31} The exact mechanism underlying the benefit is unknown but myoelectric modulation, modification of sympathovagal activity and thalamic effects have been observed. Given that there have been no reports on success or complications associated with this treatment and the pregnant population, it was not attempted.

The occurrence of gastroparesis during pregnancy can present a difficult management problem. Cases such as the one described provide an opportunity to review the treatment options and potential medical and surgical strategies for the management of severe, refractory gastroparesis.

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