Managing common luminal GI disorders during pregnancy

IAN LOCKART MB BS; **BLAKE KNAPMAN** BAppSc(MRS), DiagRad, MB BS, MRMed; **RIA KANAZAKI** MB BS; **CHRIS POKORNY** MB BS, FRACP, FRCP, FACG

Gastrointestinal disorders experienced during pregnancy, such as nausea and vomiting or gastro-oesophageal reflux, can often be controlled by lifestyle and dietary modification but medication may be needed. Women with coeliac disease or inflammatory bowel disease should have the condition under good control before becoming pregnant as active disease can adversely affect pregnancy outcomes.

KEY POINTS

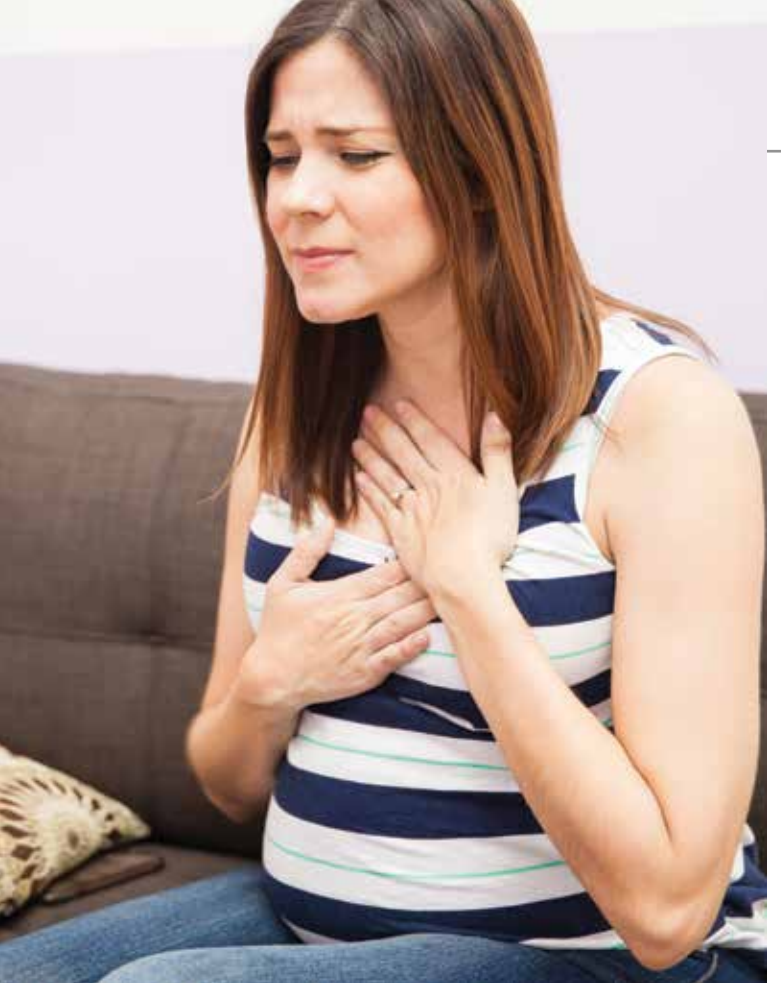
- Gastrointestinal symptoms are common in pregnancy and can result in significant morbidity.
- Some conditions, such as gastro-oesophageal reflux, may occur for the first time during pregnancy or may be exacerbated by pregnancy.
- A careful history and physical examination are essential for diagnosis.
- Nausea and gastro-oesophageal reflux may respond to lifestyle and dietary modification, although medications are often required.
- When indicated, medications should be used judiciously with knowledge of the potential risks to the fetus.
- Active coeliac disease and inflammatory bowel disease (IBD) have potential adverse effects on pregnancy outcomes.
- Recurrent miscarriages may be a clue to undiagnosed coeliac disease.
- In general, uncontrolled IBD in pregnancy poses a greater risk to the unborn fetus than many of the medications used in treatment.
- Management of IBD in pregnancy needs to be in consultation with an experienced obstetrician.

Most women will experience gastrointestinal (GI) symptoms during pregnancy (for example, nausea, vomiting, reflux, constipation and rectal bleeding. These may be pre-existing and may intensify during pregnancy, or may develop for the first time due to a range of hormonal and anatomical changes. Common conditions such as coeliac disease and inflammatory bowel disease (IBD) can have adverse potentially effects on pregnancy outcomes if the disease is active.

Dietary and lifestyle modifications can control some symptoms, and also reduce the risks of active coeliac disease, but most women with IBD will need to continue taking medication for their IBD throughout pregnancy. A thorough assessment and consideration of both maternal and fetal safety is essential before commencing or continuing any medication during pregnancy.

MedicineToday 2016; 17(11): 32-40

Dr Lockart is Conjoint Associate Lecturer at South Western Sydney Clinical School, UNSW Australia, and Gastroenterology Advanced Trainee at Liverpool Hospital, Sydney. Dr Knapman is Adjunct Associate Lecturer at Sydney School of Medicine, The University of Notre Dame Australia, and Obstetrics and Gynaecology Registrar at Royal Women's Hospital, Sydney. Dr Kanazaki is Inflammatory Bowel Disease Fellow at Liverpool Hospital, Sydney. Associate Professor Pokorny is Conjoint Associate Professor of Medicine at UNSW Australia, and Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.



This review provides a practical approach to managing common gastrointestinal symptoms and chronic gastrointestinal diseases during pregnancy.

Nausea and vomiting

Nausea is extremely common in pregnancy, affecting up to 90% of women during the early stages.[1] Some women experience mild, intermittent nausea that is manageable with dietary and lifestyle modification alone. Others develop severe and intractable vomiting referred to as hyperemesis gravidarum. Although rare, occurring in less than 1% of pregnancies, hyperemesis gravidarum can result in severe dehydration, electrolyte abnormalities, Mallory-Weiss tears and Wernicke's encephalopathy.[2,3]

When assessing pregnant women with nausea and vomiting it is important to consider differential diagnoses, pregnancy-related and otherwise. The assessment and management of women with nausea and vomiting during pregnancy is summarised in Flowchart 1. Nausea usually begins during the first trimester, peaks in severity around weeks 9 to 11, and resolves by weeks 12 to 16. A minority of women will experience symptoms that persist beyond this time.[3] Women with an atypical onset, prolonged duration or severe symptoms should be investigated for pathological causes; urinalysis, blood tests and obstetric ultrasound are appropriate investigations. Consultation with a specialist is recommended in such cases.

Nondrug therapies for nausea should be trialled initially. Reassurance should be given that nausea can be part of a normal pregnancy, is likely to resolve and will not harm their baby. Women should be advised to avoid exposure to particular foods or odours that trigger symptoms. Consuming small, frequent quantities of dry, bland foods may help, and maintaining adequate fluid intake is important. Although ginger may benefit some women with mild nausea, it is unlikely to benefit those with significant nausea or vomiting.[4] Additionally, the evidence supporting therapies such as hypnosis and acupuncture is limited.[5]

Iron is a common component of pregnancy multivitamins and may contribute to nausea. If iron supplementation is necessary and oral therapy proves intolerable then intravenous formulations, such as iron carboxymaltose, can be administered. Intravenous iron supplements should only be given in the second and third trimesters as safety data are lacking for their use during the first trimester.[6]

Nausea can also be reduced by managing concurrent gastro-oesophageal reflux disease (GORD).

Antiemetic therapy will be required for some women. Australian guidelines (Therapeutic Guidelines, *eTG Complete*, 2016) recommend starting with a combination of pyridoxine (vitamin B6) and doxylamine.[7] If symptoms persist, a short course of metoclopramide, prochlorperazine, promethazine or ondansetron is safe to add to the pyridoxine and doxylamine regimen; if vomiting continues, another drug from the list may be tried. Therapy should be individualised based on side effect profiles and effectiveness. Some practitioners reserve ondansetron as a second-line therapy and prescribe concurrent laxatives to manage constipation. Women with intractable symptoms who are unable to maintain adequate oral intake should be admitted to hospital for rehydration, electrolyte replacement and intensive symptom control.

Gastro-oesophageal reflux

GORD may occur in all three trimesters of pregnancy. An increased level of female sex hormones, in particular progesterone, leads to decreased lower oesophageal sphincter pressures. Mechanical effects of weight gain and the growing uterus during the third trimester play a minor role.[1] Women with pre-existing symptoms commonly experience an increase in frequency and severity throughout pregnancy.

Mild symptoms of GORD can generally be managed with lifestyle and dietary modification. Women should be advised to avoid foods that trigger symptoms and to eat small, frequent meals. Caffeine (coffee, tea, chocolate and soft drink) intake should also be limited, as caffeine increases gastric acid production and reduces lower oesophageal sphincter pressure. Oral intake (other than water) should be avoided for two to three hours before going to bed. Elevation of the bed head may also improve symptoms.[1] The management of women with GORD during pregnancy is summarised in Flowchart 2.

Drug therapy should be considered if symptoms do not

1. ASSESSMENT AND MANAGEMENT OF NAUSEA AND VOMITING IN PREGNANCY

Initial assessment

- History, physical examination, assess degree of dehydration
- Consider differential diagnosis:
  - pregnancy-related: early (molar pregnancy, multiple gestation), late (pre-eclampsia, acute fatty liver of pregnancy)
  - primary tract infection, gastrointestinal disorders (infection, appendicitis, pancreatitis, cholecystitis, hepatitis), neurological or vestibular disorders, endocrine disorders (calcium, urea, thyrotoxicosis), medications (iron tablets), recreational drugs (marijuana), psychological
- Consider further investigations if atypical onset, persistent or severe nausea:
  - urinalysis
  - blood tests: FBC, EUC, LFT, CMP, thyroid function, glucose (normal reference ranges for some tests vary during pregnancy)
  - ultrasound: molar pregnancy, multiple gestation

↓

Dietary and lifestyle modification

- Avoid trigger foods and odours
- Small, frequent, bland meals
- Drink small amounts of fluids often
- Ginger (consider for mild nausea)

↓

Medications

- Pyridoxine 12.5 mg mane, 12.5 mg midday, 25 mg nocte (uncategorised regarding use in pregnancy)*
  plus
  Doxylamine 25 mg nocte. Can add 12.5 mg mane and midday doses (category A)*

Can add short course of:

- Metoclopramide (category A) *or* prochlorperazine (category C) *or* promethazine (category C) *or* ondansetron (category B1)*

↓

Hospitalisation

- Intravenous fluids, electrolytes
- Intravenous antiemetics
- Thiamine supplementation
- Nutritional support

Abbreviations: FBC = full blood count; EUC = electrolytes, urea, creatinine; LFT = liver function tests; CMP = calcium, magnesium and phosphate.
* Australian categorisation system for prescribing medicines in pregnancy (https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy).

improve sufficiently with lifestyle and dietary modifications. First-line therapy is antacids. Antacids are safe to use in the recommended doses, but excessive and prolonged consumption, particularly of those containing sodium bicarbonate or magnesium trisilicate, should be avoided. Overdosage with sodium bicarbonate may result in metabolic alkalosis and fluid overload, and overdosage of magnesium trisilicate may result in fetal nephrolithiasis, hypotonia and respiratory distress.[1]

If initial therapies fail to control symptoms adequately then histamine H2-receptor antagonists should be used.[7] For women with symptoms that persist despite the use of H2-receptor antagonists, proton pump inhibitors (PPIs) can be prescribed. Although PPIs are generally considered to be safe during pregnancy, experience of their use is more limited; most local and international guidelines recommend reserving them for women with symptoms that do not respond to other therapies.[1,7]

During pregnancy, it is not recommended to test for or eradicate *Helicobacter pylori* as this bacterium does not cause GORD. However, appropriate indications for eradication may occur, such as bleeding peptic ulcer disease.[1]

Constipation

Multiple factors contribute to constipation during pregnancy. In the first trimester, decreased small bowel and colonic motility occur due to the effects of progesterone.[8] Poor water intake secondary to nausea as well as medications such as iron and ondansetron may also contribute. Later in pregnancy, pressure on the rectosigmoid colon from the gravid uterus and a decrease in physical exercise also play a role. Other diseases to consider when evaluating women reporting constipation include pre-existing irritable bowel syndrome and hypothyroidism.

Treatment of constipation in pregnant women is similar to that in the nonpregnant population. Adequate water intake, a high-fibre diet and light physical exercise are often sufficient. Women should be advised to pass a motion whenever they feel the urge. If required, laxative medications have minimal systemic absorption and are safe to use, although short-term use is recommended to avoid dehydration and electrolyte imbalance. Initial treatment should be with a bulk-forming agent (a fibre supplement such as psyllium) or an osmotic laxative (lactulose, macrogol 3350 with electrolytes, or sorbitol; magnesium-containing laxatives [Epsom salts] are best avoided in pregnancy). Stool softeners such as docusate can also be used. Stimulant laxatives (e.g. senna) are not recommended for first- line therapy.[7]

Rectal bleeding

Rectal bleeding occurs in about one-third of pregnant women, commonly due to bleeding internal haemorrhoids.[1] Anal fissures

2. MANAGEMENT OF GASTRO-OESOPHAGEAL REFLUX IN PREGNANCY

Dietary and lifestyle modification
- Avoid foods that trigger symptoms and caffeine
- Eat small, frequent meals
- Avoid oral intake (other than water) for 2 to 3 hours before bed time
- Bed head elevation

Medications
- Antacids
  - considered safe to use in recommended doses
- H2-receptor antagonists
  - ranitidine, famotidine (both category B1)*
  - nizatidine (category B3)*
- Proton pump inhibitors
  - rabeprazole (category B1)*
  - omeprazole, pantoprazole, lansoprazole, esomeprazole (all category B3)*

* Australian categorisation system for prescribing medicines in pregnancy (https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy).

and more sinister aetiologies should also be considered (Box). A comprehensive history and physical examination will provide important clues. Anal fissures generally cause significant pain on defaecation. Infective causes may present with bloody diarrhoea associated with nausea, vomiting, fevers and abdominal cramps. Inflammatory bowel disease, although unlikely, should be considered if there is accompanying pain, mucus in the stool, urgency to defaecate, extra-intestinal manifestations (joints, eyes, skin) or a history of recurrent bouts of bloody diarrhoea. If the cause of rectal bleeding is unclear from clinical assessment, flexible sigmoidoscopy can be performed with minimal maternal and fetal risk (see endoscopy section later in article).

The management of haemorrhoids during pregnancy is generally conservative because they usually resolve after delivery. Women should be advised to increase dietary fibre intake and ensure adequate water intake. A stool softener, such as docusate, can be used to avoid constipation. Irritation and pruritus can be managed with a range of topical analgesics and corticosteroids, but creams and suppositories containing hydrocortisone should not be used for longer than one week. Surgical procedures should be delayed until the postpartum period whenever possible. If absolutely required during pregnancy, surgical procedures such as rubber band ligation can be used after considering the risks and benefits.[1,9]

1. CAUSES OF RECTAL BLEEDING IN PREGNANCY

Common	Uncommon
• Anal fissures	• Colorectal malignancy/polyps
• Haemorrhoids	• Diverticular disease
	• Infectious colitis
	• Inflammatory bowel disease
	• Ischaemic colitis

Coeliac disease

Coeliac disease is the most common autoimmune disease in Australia, affecting at least 1% of the population (Figure 1). Pregnant women with coeliac disease should be made aware of the potential adverse outcomes of active disease, including preterm delivery, low birthweight, small-for-gestational-age infants and intrauterine growth restriction. Miscarriages are not uncommon in women with untreated coeliac disease; when they are recurrent, this condition needs to be excluded.

Adhering to a gluten-free diet reduces the pregnancy-related risks associated with coeliac disease. In addition, nutritional deficiencies that occur with coeliac disease should be monitored and treated during pregnancy and fetal growth regularly assessed.[10]

Inflammatory bowel disease

Women with IBD can have normal pregnancies. Outcomes are most favourable when women are in remission at the time of conception and maintain this throughout pregnancy.[11] Having active disease, especially at the time of conception, increases the rates of adverse outcomes including preterm delivery, low birthweight and small for-gestational-age infants.[12,13]

Preconception counselling should be routine for all women of reproductive age with IBD. Disease activity should be assessed before attempting to conceive, and therapy modified to achieve and maintain clinical and endoscopic remission. As there is often a poor correlation between symptoms and endoscopic disease activity, particularly in patients with Crohn's disease, objective measures should be used.[13] Endoscopy, faecal calprotectin testing and small bowel imaging (for Crohn's disease) can help guide important treatment decisions (Figure 2). For women with active disease, delaying conception until remission is achieved is advisable.

Most drugs used in the treatment of patients with IBD are safe to use throughout pregnancy, including 5-aminosalicylate preparations (5-ASAs; oral and rectal; balsalazide, mesalazine, olsalazine), sulfasalazine and thiopurines (azathioprine, mercaptopurine; both used off label for IBD), as summarised in the Table.[11,12] Sulfasalazine interferes with folate absorption and during pregnancy the normal folic acid supplementation for patients taking sulfasalazine (1 mg daily) should be increased;

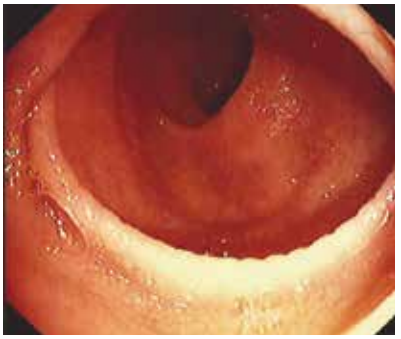


Figure 1. Coeliac disease, showing scalloping of duodenal folds. Potential adverse outcomes of active disease in pregnancy include preterm delivery, low birthweight, small-for-gestational-age infants and intrauterine growth restriction.

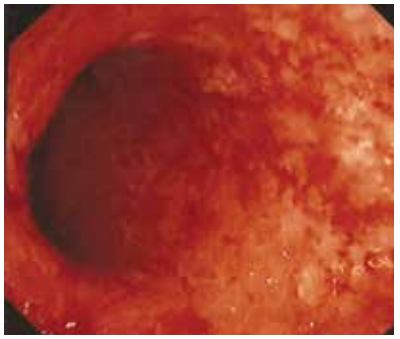


Figure 2. Severely active ulcerative colitis. Endoscopy helps guide treatment decisions in women with inflammatory bowel disease who are planning pregnancy. Delaying conception until remission is achieved is advisable.

most guidelines recommend 2 mg daily during pregnancy, although the eTG 2016 recommends a higher dose of 5 mg daily.[7] (The normal recommended folic acid supplementation dose for pregnant women is 0.5 mg daily or a multivitamin containing folic acid 0.4 mg or more daily.[7]) Methotrexate is the obvious exception, being a teratogen; it is contraindicated during pregnancy and should be ceased four to six months before planned conception. If pregnancy occurs while taking methotrexate, it should be discontinued immediately, high dose folate therapy commenced and early obstetric consultation obtained to discuss therapeutic abortion. Methotrexate's maximal teratogenic effects occur between weeks 8 and 10 of gestation.[11] This drug should also be avoided by men before planned conception as it causes reversible oligospermia.[11]

Women who develop a disease flare during pregnancy can often be managed through optimisation of medical therapy (5-ASAs, sulfasalazine, thiopurine). Corticosteroids (usually oral prednisolone) are safe to use when required, but may increase the risk of hypertensive disorders and diabetes. Some women with severe flares will require biologic therapy or even surgery. Current evidence suggests that antitumour necrosis factor (anti-TNF) agents (infliximab, adalimumab) are not associated with significant maternal or neonatal adverse outcomes, but long-term safety has not yet been established.[14] If anti-TNF agents are given during pregnancy, the infant should not receive live vaccines during the first 12 months of life. Endoscopy or surgery should not be delayed during pregnancy if they are indicated.[13]

TABLE. IBD MEDICATIONS CONSIDERED SAFE TO USE DURING PREGNANCY

Drug	Medicines in pregnancy category*	Comments
Sulfasalazine	A	Low risk; higher dose folic acid supplementation recommended
5-Aminosalicylate preparations		
Balsalazide	C	Low risk
Mesalazine	C	
Olsalazine	C	
Thiopurines		
Azathioprine	D	Off-label use for IBD Category D because of animal data suggesting teratogenicity at high IV doses
Mercaptopurine	D	
Corticosteroids		
For example, prednisolone	Generally A	Safe to use when required but may increase the risk of hypertensive disorders and diabetes
Anti-TNF agents		
Adalimumab	C	Long-term safety not yet established
Infliximab	C	

Abbreviations: Anti-TNF = antitumour necrosis factor; IBD = inflammatory bowel disease.
* Australian categorisation system for prescribing medicines in pregnancy (https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy).

The method of childbirth in women with IBD should be decided using a multidisciplinary approach. The primary considerations should be obstetric indications and patient preference. For some women caesarean section will be recommended, in particular those with active perianal Crohn's disease or active rectal inflammation, to reduce the risk of perianal injury; it may also be recommended for women with an ileal pouch–anal anastomosis (IPAA; also called a 'J pouch'). Vaginal delivery remains an option for women with a colostomy or ileostomy.[12]

Corticosteroids, 5-ASAs, sulfasalazines, thiopurines and anti-TNF agents are safe to use when breastfeeding. Methotrexate, however, is contraindicated.[13]

Safety of endoscopy during pregnancy

Gastrointestinal endoscopic procedures are generally considered safe during pregnancy but should only be performed if there is

a strong indication (such as significant gastrointestinal bleeding, undiagnosed IBD, suspected gastrointestinal malignancy or symptomatic choledocholithiasis) or results are required to inform treatment decisions. Most guidelines recommend deferring endoscopy until the second trimester when possible.[12] General risks such as perforation, bleeding and infection need to be considered.

The risks to the fetus of endoscopy also need to be acknowledged and preventive measures taken. Women in the second and third trimester should be placed in the left pelvic tilt or left lateral position to avoid vascular compression leading to decreased uterine blood flow and fetal hypoxia.

The sedative drug used in endoscopic procedures should be selected carefully, and oversedation should be avoided as it can result in maternal hypotension and hypoxia.

If appropriate, flexible sigmoidoscopy should be chosen over colonoscopy. Flexible sigmoidoscopy can be performed with shorter procedure time, minimal to no sedation and without complete bowel preparation.[13]

Conclusion

Gastrointestinal symptoms can be debilitating during pregnancy and affected patients may require hospitalisation. A comprehensive assessment is essential and differential diagnoses must be considered. Lifestyle measures will provide adequate relief for some women but others will require drug therapy.

Women with IBD should have their disease activity assessed prior to attempting to conceive. Therapy should be optimised to achieve remission at conception and throughout pregnancy. Most medications used for inflammatory bowel disease are safe to continue during pregnancy and while breastfeeding. MT

References

1. van der Woude CJ, Metselaar HJ, Danese S. Management of gastrointestinal and liver diseases during pregnancy. Gut 2014; 63: 1014-1023.
2. Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. BMJ 2011; 342: d3606.
3. Lowe S. It's not just morning sickness. How should we manage nausea and vomiting in pregnancy? O&G Magazine 2012; 14: 31-33.
4. Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J 2014; 13: 20.
5. Matthews A, Haas DM, O'Mathuna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 2015; (9): CD007575.
6. Kidson-Gerber G, Zheng S. Iron deficiency in pregnancy: what you need to know. Med Today 2016; 17(4): 41-46.
7. eTG complete. Melbourne: Therapeutic Guidelines Limited; 2016. Available online at: https://tgldcdp.tg.org.au (accessed November 2016).
8. Keller J, Frederking D, Layer P. The spectrum and treatment of gastrointestinal disorders during pregnancy. Nat Clin Pract Gastroenterol Hepatol 2008; 5: 430-443.
9. Wald A. Constipation, diarrhea, and symptomatic hemorrhoids during pregnancy. Gastroenterol Clin North Am 2003; 32: 309-322.
10. Tersigni C, Castellani R, de Waure C, et al. Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. Hum Reprod Update 2014; 20: 582-593.
11. Bell S. Pregnancy and inflammatory bowel disease: what to do with the medication? Med Today 2016; 17(8): 73-75.
12. van der Woude CJ, Ardizzone S, Bengtson MB, et al; European Crohn's and Colitis Organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis 2015; 9: 107-124.
13. Nguyen GC, Seow CH, Maxwell C, et al; IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. Gastroenterology 2016; 150: 734-757.e1.
14. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology 2016; 151: 110-119.

COMPETING INTERESTS: None.

Ask an expert

Puzzled by a presentation? Is the diagnosis a dilemma? What would a specialist in the relevant field do? Send us your baffling or hard-to-treat general practice cases for consideration in our 'Clinical case review' series. The case synopsis should be no longer than 150 words and include one or two specific questions that you want answered.
Write to:
Medicine Today, PO Box 1473, Neutral Bay NSW 2089
or editorial@medicinetoday.com.au