CASE REPORT

Salvage therapy for acute severe ulcerative colitis during pregnancy

Manjri Raval,¹ Matthew C Choy,^{2,3} Peter De Cruz^{2,3}¹General Medicine, Austin Health, Heidelberg, Victoria, Australia²Gastroenterology, Austin Health, Heidelberg, Victoria, Australia³The University of Melbourne, Melbourne, Victoria, Australia**Correspondence to**Dr Peter De Cruz,
ppdecruz@gmail.com

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SUMMARY

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with an age of onset that affects young people during the peak of their reproductive years. Management of flares of disease during pregnancy can be complex and there are few case reports of pregnant women with acute severe ulcerative colitis (ASUC). We present the case of a 31-year-old pregnant woman who at 16 weeks gestation developed ASUC in the context of primary non-response to infliximab therapy. She subsequently underwent an emergency laparoscopic colectomy after failing to respond to hydrocortisone and cyclosporine salvage therapy. Her pregnancy was further complicated by HELLP (Haemolysis, Elevated liver enzymes and Low Platelets) syndrome resulting in premature delivery at 27 weeks gestation. This case highlights the management issues involved in ASUC during pregnancy and the assessment of disease activity, use of salvage therapies, and provides a framework to approach this complex medical emergency.

BACKGROUND

Acute severe ulcerative colitis occurs in 20% of patients during the course of their disease.¹ A third of patients do not respond to first line therapy with hydrocortisone and fifty percent of patients do not respond to cyclosporine or infliximab salvage therapy.² Up to thirty percent of patients require emergency colectomy within 3 months of their admission.¹ The risk of a significant flare of ulcerative colitis is increased especially after delivery but can occur at any time during pregnancy.^{2,3} A severe flare of UC during pregnancy poses significant risks to both mother and fetus.^{4,5} Active disease in pregnancy is the biggest driver of adverse outcomes such as an increased incidence of stillbirth, preterm delivery and postpartum complications for both the mother and neonate.^{6–8}

The literature regarding the optimal management of ASUC during pregnancy is limited. There are few case reports describing the outcomes of salvage therapy and surgery for refractory ulcerative colitis in pregnancy. Although surgery should only be undertaken in an emergency situation for ASUC during pregnancy we sought to provide a framework for the management considerations associated with this medical emergency during pregnancy to minimise the risk to the mother and baby.

CASE PRESENTATION

A 31 year old woman G1P0 (16/40) with a 3 year history of chronic active ulcerative colitis refractory to aminosalicylate (4g/day), azathioprine (150mg/day) and infliximab induction therapy (administered at weeks 0,2 and 6) presented to antenatal clinic at 16 weeks gestation with a flare of disease activity which was characterised by increased stool frequency up to 10 bowel actions per day, bloody diarrhoea, 'crampy abdominal pain', fevers and chills. She had lost 10kg of weight over the preceding 2 years. There was no significant past history nor was there a family history of inflammatory bowel disease (IBD). On presentation she was febrile to 38 degrees Celsius, with a PR 90 bpm and a BP 102/70. She appeared cachectic. Abdominal and cardio-respiratory examination were unremarkable. Fundal height was 16 cm and the fetal heart rate was auscultated at 140 beats per minute.

INVESTIGATIONS

On admission routine blood tests indicated: severe anaemia - Hb 52 (115–165 g/L); leucopenia - white cell count 2.6 (4.0–11×10⁹/L); Platelets 289 (150 - 400), and; hypoalbuminaemia - albumin - 17 (35–52 g/L); C-Reactive Protein 103.5 (<5.0 mg/L), and; Erythrocyte sedimentation rate - 138 (7–18 mm/hr). She therefore met all the criteria for acute severe ulcerative colitis based on the Truelove and Witts criteria (table 1).

Faecal microbiology/culture/sensitivity and Clostridium difficile toxin were negative. Abdominal X-ray excluded a toxic megacolon and flexible sigmoidoscopy revealed Mayo three colitis characterised by a continuous area of bleeding, ulcerated mucosa which was present continuously from the rectum to the sigmoid colon and beyond to the limit of insertion at the splenic flexure (figure 1). Histology confirmed chronic active ulcerative colitis with no evidence of granulomas nor dysplasia and excluded cytomegalovirus (CMV) inclusion bodies. Infliximab trough levels were at 3.9 microgram/ml indicating primary non-response to infliximab.

DIFFERENTIAL DIAGNOSIS

An infectious precipitant was excluded based on a normal faecal microscopy and culture and negative clostridium difficile enterotoxin assay and absence of CMV inclusions on histology. The underlying diagnosis of severe ulcerative colitis (Mayo 3) was confirmed at flexible sigmoidoscopy.

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Table 1 Truelove and Witts' classification of severity of ulcerative colitis on admission

Variable	Mild	Moderate	Severe
Number of bloody stools per day	<4 per day	4–6 per day	>10 per day
Temperature	Apyrexial	Intermediate	>37.8
Heart rate bpm	Normal	Intermediate	>90 bpm
Haemoglobin level g/dl	>11	10.5–11	<10.5
Erythrocyte sedimentation rate (mm/h)	<20	20–30	>30 mm/h

Oxford index is defined as: >8 stools per day OR >2 stools per day and plasma C-reactive protein (CRP) concentration >45 mg/L following 3 days of IV steroids (which is associated with an 85% positive predictive value for colectomy)

TREATMENT

The patient underwent a transfusion of 3 units of packed red blood cells. She failed to respond to 5 days of intravenous hydrocortisone 100 mg four times per day and 3 days of cyclosporine salvage therapy and subsequently underwent emergency laparoscopic colectomy (figure 2).

OUTCOME AND FOLLOW-UP

Postoperatively the patient developed hospital acquired pneumonia that improved after 5 days of intravenous ceftriaxone followed by an oral course of antibiotics (Amoxycillin & Clavulanic acid). At 27 weeks gestation she developed HELLP syndrome that precipitated an emergency caesarean. Her newborn required monitoring in neonatal intensive care following preterm delivery, was small for gestational age and born with a strabismus and subsequently diagnosed with cerebral palsy. Despite a pregnancy complicated by emergency colectomy and HELLP syndrome the patient recovered well and has planned to defer her ileal pouch anal anastomosis (IPAA) until she completes her family planning in order to reduce the risk of pouch surgery on her fecundity.

DISCUSSION

This case highlights the complexities associated with the management of ASUC in pregnancy. Ulcerative colitis is generally more likely to flare up early post delivery but may occur at any time during pregnancy.⁶ Disease activity improves in approximately 1/3 of patients; remains stable in 1/3 and worsens in 1/3 of cases during pregnancy. The biggest driver of adverse outcomes in pregnant women is active disease therefore, active medical

Figure 2 Image of resected bowel

management is considered to be justified.⁸ The management and treatment of ulcerative colitis during pregnancy must take into consideration the risks and benefits of treatment associated with each trimester.^{9–12}

A risk factor for a flare of severe ulcerative colitis is active disease at the time of conception. Disease in remission at the time of conception has conversely been associated with improved outcomes and reduces the risk of complications during pregnancy.^{9 13 14} Unfortunately in the case of our patient she had active disease at the time of conception which limited her treatment options. The patient was being treated with mesalazine 4g/day, azathioprine 150mg/day, infliximab 8 weekly, and budesonide enemas as required prior to conception and at the time of her initial admission. Optimal management should ideally commence with preconceptual counselling with the aim of inducing remission prior to conception. Reassessment of disease activity should ideally take place prior to conception in order to inform therapeutic decision making during pregnancy. In the case of our patient the consequences of uncontrolled active disease included pre-term birth, low birth weight for gestational age, cerebral palsy and emergency colectomy.

Assessment of the patient with acute severe colitis

The assessment of a patient with ASUC requires input from gastroenterologists, colorectal surgeons and obstetricians. Careful clinical evaluation is required to discern disease severity based on combination of clinical examination and biochemical parameters (haemoglobin, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and albumin; exclusion of infectious precipitants with stool cultures and *Clostridium difficile* toxin assay is also warranted). In the case of our patient there was a discordance between her reported symptoms and her severity of presentation. Although it is acknowledged that she was both anaemic and hypoalbuminaemic, both haemoglobin and albumin are known to be mildly reduced in normal pregnancy. It is important to take the known reductions in haemoglobin and albumin in pregnancy into consideration when assessing disease severity.

The use of radiological investigations such as abdominal X-rays is permissible where there are features to suggest systemic toxicity in order to exclude toxic megacolon. A CT/MRI is not routinely required unless there is a high index of suspicion of intraabdominal sepsis or penetrating complications.¹⁵ Intestinal ultrasound is an evolving modality in the assessment of

Figure 1 Image of flexible sigmoidoscopy

inflammatory bowel disease. In experienced hands it may also be used to concurrently assess the viability of the fetus.

Investigation with flexible sigmoidoscopy to investigate the extent and severity of colitis in patients during pregnancy is safe among patients with acute severe ulcerative colitis and should be performed by experienced endoscopists.^{15 16} A biopsy should be obtained in order to exclude CMV based on presence of inclusion bodies and immunohistochemistry. Monitoring fetal status and heart rate is recommended during invasive procedures and surgery.¹⁵

Medical therapy

First line therapy for patients with ASUC includes hydrocortisone which is considered safe in pregnancy in the second and third trimesters. Corticosteroids are associated with a low risk of lip-jaw palate cleft in the first trimester. Antibiotics are not indicated unless a specific pathogen is isolated.

There are a limited number of cases that have reported the use of salvage therapies for acute severe ulcerative colitis in pregnant women.^{9 17–23} Patients should be assessed for the need for salvage if there is a failure to respond to 3 days of IV hydrocortisone based on objective indices such as the Oxford index is defined as: >8 stools per day OR >2 stools per day and plasma CRP concentration >45 mg/L following 3 days of IV steroids (which is associated with an 85% positive predictive value for colectomy). Both infliximab salvage therapy and cyclosporine are pregnancy class B drugs. Both salvage therapies are equally effective in the setting of ASUC. Anti-TNF therapy is not associated with an increased risk of adverse pregnancy outcomes, congenital abnormalities, or preterm birth compared with the general population.²⁴

Tacrolimus has also been successfully used in pregnancy with the delivery of a healthy baby spontaneously at 40 weeks gestation and maintenance of a stable remission of ulcerative colitis.¹⁵ Specific risks of calcineurin inhibition in pregnancy include increased risk of electrolyte disturbance, and blood pressure monitoring. It is contraindicated in preeclampsia and renal impairment. These salvage therapies are effective in 50% of patients.²⁴

Colectomy is recommended in patients who fail to respond to salvage therapy within 7 days.²⁵ However, in carefully selected cases in specialised centres, second line salvage therapy with either sequential infliximab or cyclosporine can be considered. A recent meta-analysis of sequential therapy reported a short-term treatment response rate of 62.4% (95% CI (CI), 57.0%–67.8%) and remission in 38.9% (95% CI, 33.5% to 44.3%).²⁶ However, extreme caution should be taken due to the risk of serious infectious complications and mortality and the low quality of available data.^{25 26} To our knowledge, no data on sequential therapy exists in pregnancy. In the case of our patient she was found to have active disease despite an infliximab trough level of 3.9microgram/ml indicating that she was a primary non-responder to infliximab. She was therefore treated with cyclosporine after a discussion about the risk versus benefit of sequential therapy. She developed pneumonia in the setting of sequential therapy and failed to respond to cyclosporine.

Following successful induction patients require appropriate maintenance therapy which can be determined by the treatment history and disease course. Aminosalicylates (5-ASA) are a common component of maintenance therapy and are pregnancy class B. Rare cases of diarrhoea in breastfed infants have been reported but have not been considered sufficiently significant to stop its use.¹⁵ A risk of patent ductus arteriosus

in the third trimester has been found in mice exposed to 5-ASA hence women should be counselled and offered the choice of ceasing 5-ASA in their third trimester. Women taking sulfasalazine should take folic acid supplementation to reduce the risk of neural tube defects.¹⁵

Thiopurines such as azathioprine and 6-mercaptopurine are considered safe in pregnancy and should be continued following salvage therapy.^{15 16} These are minimally transferred into breast milk and thought to be safe in breastfeeding.^{15 16}

Category X drugs such as methotrexate should not be used in pregnancy and women are recommended to discontinue methotrexate at least 6 months before conception.¹⁵

In addition to induction therapy, anti-TNF treatment can be utilised as maintenance therapy in ulcerative colitis and has not been associated with increased adverse pregnancy outcomes in a recent meta-analysis.^{24 27–36} Vedolizumab is also effective in ulcerative colitis; however, there is insufficient experience to guide recommendations on its routine use in women considering pregnancy.²⁸

Patients with IBD should receive thromboprophylaxis after caesarean section or delivery especially if there is active disease due to the high risk of venous thromboembolism. Low molecular weight heparin is recommended over unfractionated heparin.

A caesarean section should be considered as the mode of delivery among those patients who are considering an IPAA to reduce the risk of anal sphincter injury/dysfunction. Surgical management is reserved for acute severe ulcerative colitis that is refractory to salvage therapy, toxic megacolon, intractable haemorrhage and perforation of the colon. There are higher risks of spontaneous abortion if undertaken during the first trimester.

Patient's perspective

'Coping with a chronic illness and undergoing major surgery at any time was a daunting experience but doing so while pregnant magnified it. The great concern I had while trying to treat the UC was the numerous drugs I was putting into my body. I understand those drugs were necessary but it was hard not knowing what the side effects to the baby would be and it was something I was not keen on doing throughout the rest of the pregnancy.'

Having surgery was obviously the last option but one that has improved my quality of life. All the doctors involved in my case were fantastic and I knew I was in the best hands.'

Learning points

- ▶ Management of women with ulcerative colitis should ideally begin prior to conception.
- ▶ The biggest driver of adverse pregnancy outcomes is uncontrolled active disease.
- ▶ Flares of active disease require careful assessment of disease severity and prompt initiation of medical therapy.
- ▶ Hydrocortisone should be the first line therapy for ASUC.
- ▶ Salvage therapy such as infliximab and cyclosporine are equally effective and safe in pregnancy and should be considered among patients refractory to hydrocortisone.
- ▶ Surgery is indicated for patients with severe colitis non-responsive to medical management.
- ▶ Following colectomy the optimal timing of pouch surgery should be discussed due to its potential impacts on fecundity.

There are increased risks of fetal distress, preterm delivery as well increased maternal and fetal morbidity/mortality if undertaken during the third trimester.¹⁰ Surgery therefore is safest when undertaken in second trimester. Delivery at the same time of surgery needs to be considered based on the time of gestation.³⁷ Contrary to previous reports which suggested an increased risk of fetal death and maternal morbidity, more recent case reports suggest a colectomy for severe ulcerative colitis during pregnancy can be undertaken safely.^{37–41} Our patient failed to respond to sequential therapy hence underwent colectomy in the second trimester (18 weeks gestation). She was given steroids to promote fetal lung maturation and her baby was delivered at 27 weeks gestation following the development of HELLP.

Following colectomy it is important to consider the impact of IPAA on fecundity. Women who desire to continue family planning may elect to have their pouches performed after completing their family to reduce the impact of surgery on their fertility. Management in such cases requires a multidisciplinary team approach. Our patient is currently 23 weeks pregnant in her second pregnancy and has deferred IPAA until she has completed her family.

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