

Single Case

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# A Patient with Crohn's Disease Who Gave Birth Despite Sigmoid Volvulus, Venous Thrombosis, Nontraumatic Fracture of the Rib, and Sepsis during Pregnancy

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## Keywords

Refractory Crohn's disease · Pregnancy · Bowel obstruction · Nontraumatic fracture · Thrombosis · Sepsis

## Abstract

The patient was a woman in her 40s who was diagnosed with Crohn's disease (CD) of the large and small intestines in 1996. In 2005, she was referred to our hospital for treatment. We treated her for 17 years with corticosteroids, biologics, immunosuppressive agents, 5-aminosalicylic acid, and nutrition care. However, her Crohn's Disease Activity Index remained between 200 and 250, indicating refractory CD. During her medical treatment, the patient also underwent 3 operations. One year ago, the patient became pregnant through in vitro fertilization. Even after pregnancy was confirmed, the patient continued her treatment for refractory CD with ustekinumab, granulocyte apheresis, and budesonide. Nonetheless, her CD was highly active during pregnancy, and she experienced various complications: sigmoid volvulus at gestational week 15, venous thrombosis at gestational week 17, nontraumatic rib fracture due to fetal movement at gestational week 32, and sepsis from central venous catheter infection at gestational week 37. At gestational week 38, the patient gave birth by emergency cesarian delivery. This paper reports details of the case in which delivery was achieved after various complications were overcome and discusses previous relevant reports.

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## Introduction

The number of patients with inflammatory bowel disease (IBD) has been increasing in recent years. Accordingly, physicians often encounter patients with IBD, which is generally a refractory disease [1]. Research has shown that fertility, pregnancy, and delivery are not different in patients with and without IBD, although the pathological state of Crohn's disease (CD) may affect pregnancy and delivery. Therefore, it is recommended that patients with IBD conceive once remission is established [2]. CD, a subtype of IBD, commonly develops when patients are young [3], so it may often impact pregnancy and delivery in female patients.

Here, we report on a patient with refractory CD who conceived by in vitro fertilization and experienced various complications during pregnancy, including sigmoid volvulus, venous thrombosis, nontraumatic rib fracture, and sepsis. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000531705>).

## Case Report

The patient was a woman in her 40s with a 26-year history of refractory CD of the small and large intestines. At diagnosis, the patient's Crohn's Disease Activity Index (CDAI) was 260–300, indicating severe CD [4]. Initially, a corticosteroid and azathioprine (AZA) were administered to achieve remission. However, AZA-related pancytopenia developed, so the drug had to be discontinued. No biologics were available for clinical use at that time, so the patient was treated with 5-aminosalicylic acid and enteral feeding. However, bowel inflammation recurred repeatedly and was treated with a corticosteroid.

Nine years after being diagnosed with CD, the patient underwent subtotal bowel resection (ileosigmoidostomy) because of bowel stenosis. Postoperatively, an anti-tumor necrosis factor preparation, infliximab (IFX), was administered.

Sixteen years after diagnosis of CD, small intestinal stenosis was detected, and laparoscopy-assisted partial intestinal resection was performed (length of residual small intestine: 185 cm). The efficacy of IFX was considered to be insufficient, so the patient was switched to another anti-tumor necrosis factor preparation, adalimumab (ADA).

Nineteen years after the initial diagnosis of CD, stenosis occurred at the anastomosed ileum-sigmoid site, and the stenotic lesion was excised. Postoperatively, ADA therapy was continued at an increased dose, but the CDAI remained at 240 to 260, indicating persistence of moderate inflammation. After the operation, the patient's ova were cryopreserved.

At the same time, the efficacy of ADA was also considered insufficient, and the patient was switched to ustekinumab, an interleukin 12/23p40 monoclonal antibody preparation. During combined treatment with ustekinumab and budesonide, the CDAI was 210–230. During this period, the patient became pregnant by means of intracytoplasmic sperm injection into cryopreserved ova and blastocyst transfer into the uterus. When the patient was found to be pregnant, she was 158 cm tall and weighed 40.5 kg (BMI, 16.2), and the CDAI was 220–230. The YAM (Young Adult Mean) and T-score at this time were 67% and –2.5, respectively, lower.

The patient continued to take ustekinumab continuously during pregnancy. On day 1 of gestational week 15, she suddenly developed nausea, vomiting, and abdominal pain in the left lower quadrant and was admitted to our hospital. She had had no bowel movement for the previous 2 days. At admission, she weighed 42 kg, and her blood pressure was 94/52 mm Hg; pulse rate, 76/min; and temperature, 37.2°C. Her clinical symptoms were abdominal distention and moderate spontaneous pain and tenderness, mainly in the subumbilical region. A perianal abscess was noted. Hematological tests revealed an elevated C-reactive protein level

of 3.79 mg/dL. Serum biochemistry tests revealed decreased levels of albumin (2.4 g/dL) and hematocrit (32%). No abnormality was found in hepatic or renal functions or in bleeding and coagulation parameters. Fecal culture revealed no abnormalities (Table 1).

To investigate the pathogenesis of the abdominal pain, abdominal X-ray examination and computed tomography (CT) scan were performed (Fig. 1). Marked intestinal gas was seen, and the CT scan revealed sigmoid volvulus. In addition, a 14-cm-long fetus was observed in the distended uterus. Emergency colonoscopy was performed under fluoroscopic guidance to release the volvulus (Fig. 2). Colonoscopy also revealed a stenosis on the anal side of the ileosigmoidostomy site. On the oral side of the anastomosed site, reddening, mucosal edema, and a longitudinal ulcer were observed. These lesions were considered to be due to active CD. Therefore, budesonide was administered again on an inpatient basis from gestational week 16, and granulocyte-monocyte apheresis (GMA) was initiated from gestational week 17 to treat lesions in the residual colon [5]. However, after the second session of GMA, reddening and pain developed in the ulnar vein, and transdermal ultrasound revealed thrombosis. Therefore, GMA was discontinued, and heparin therapy was started.

The patient was discharged in gestational week 18. Heparin was continuously administered at home, and the thrombosis disappeared in gestational week 28, at which time the CDAI was 230–240.

In gestational week 32, the patient suddenly felt severe pain in the left thoracoabdominal region towards the shoulder, and she came to the emergency department of our hospital. The medical examination revealed a body weight of 42 kg, blood pressure of 140/64 mm Hg, pulse rate of 114/min, and body temperature of 37.0°C. She had a bowel movement 2 to 3 times a day, and the abdominal region was distended, mainly in the subumbilical area; the pain score on the Numerical Rating Scale (NRS) was 10/10 in the left thoracoabdominal region [6]. Inspiration caused severe pain in that region, and she stated that she had felt a strong fetal movement just before the pain started. Stomatitis and a perianal abscess were noted. Hematological tests revealed an increase in the white blood cell count to  $11.16 \times 10^3/\mu\text{L}$  and in C-reactive protein to 3.21 mg/dL and a decrease in hemoglobin to 8.5 g/dL, hematocrit to 26%, and albumin to 2.7 g/dL. Hepatic and renal functions and bleeding and coagulation parameters showed no abnormalities. Electrocardiography was normal, and tests for myocardial troponin T, creatine kinase-MB, and troponin I were negative. From these findings, acute coronary syndrome was ruled out (Table 1). The chest X-ray film revealed a fracture of the left seventh rib (Fig. 3) that was not related to an external injury but was considered to be related to fetal movement. The patient was instructed to rest in bed and take oral acetaminophen, which together controlled her chest pain. Subsequently, the thrombosis in the ulnar vein disappeared, and one session of GMA was performed in gestational week 34 to treat CD.

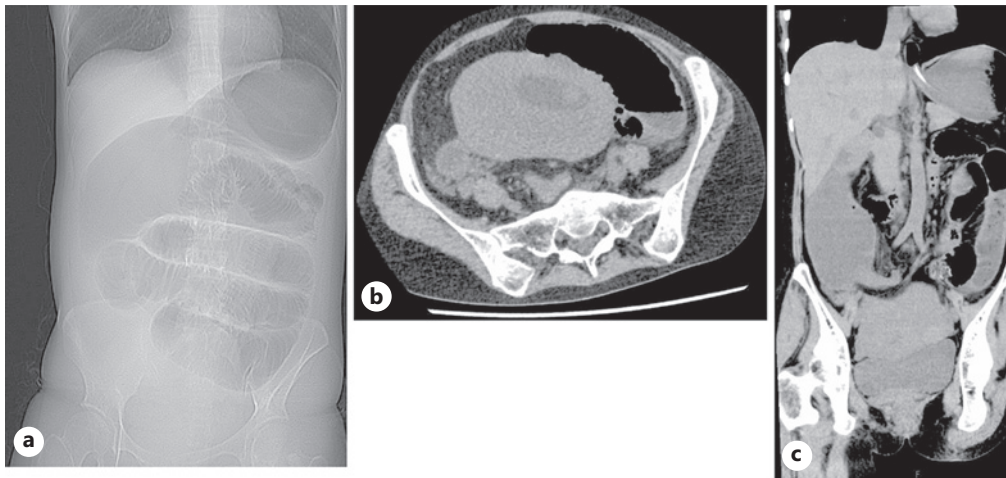
On day 2 of gestational week 37, the patient developed a fever of 39°C, and reddening was noted at the insertion site of the central venous catheter. Blood culture revealed the presence of Gram-negative bacilli (Table 1). We considered that sepsis had developed as the result of a catheter infection, so the catheter was removed and antibiotic therapy (daptomycin) was started.

On day 2 of gestational week 38, another bowel obstruction occurred. We considered it difficult for the patient to maintain the pregnancy, so an emergency cesarian delivery was performed by a midabdominal incision on day 3 of gestational week 38. The baby was a girl weighing 2,250 g with an Apgar score of 9/9. The patient's intestine was found to be slightly distended, but no obvious torsion was observed. The patient's postpartum course was uneventful, although symptoms of abdominal distention remained, and she was thus discharged. GMA was resumed in postpartum week 2 and ustekinumab therapy in postpartum week 6. The CDAI remained at around 200 during the first 6 months postpartum.

**Table 1.** Blood sample findings

General blood tests	Gestational week 15, day 1	Gestational week 32, day 0	Gestational week 37, day 2
WBC,/ $\mu$ L	$6.96 \times 10^3$	<u>11.16</u> $\times 10^3$	<u>10.68</u> $\times 10^3$
NEUT, %	10.8	<u>77.9</u>	<u>88.8</u>
LYMPH, %	5.7	14.8	<u>6.0</u>
Hb, g/dL	<u>9.5</u>	<u>8.5</u>	12.1
HCT, %	<u>31.1</u>	<u>26</u>	35.7
Plt,/ $\mu$ L	$25.1 \times 10^4$	$26.2 \times 10^4$	$27.5 \times 10^4$
Special blood tests			
TP, g/dL	<u>5.9</u>	6.9	6.8
ALB, g/dL	<u>2.4</u>	<u>2.7</u>	3.8
T-Bil, mg/dL	0.5	0.4	0.6
AST, U/L	22	31	33
ALT, U/L	17	28	28
ALP, U/L	227	<u>598</u>	<u>127</u>
$\gamma$ GTP, U/L	18	46	8
Amy, U/L	116	<u>24</u>	18.7
Lip, U/L	33	<u>0.8</u>	0.74
BUN, mg/dL	8.8	62.8	67.3
Cre, mg/dL	0.73	0.8	0.74
eGFR, mL/min	69.2	62.8	67.3
TG, mg/dL			177
LDL, mg/dL			65
Na, mEq/L	140	135	139
K, mEq/L	<u>3.0</u>	4.7	4.0
CL, U/L	108	104	103
CRP, mg/dL	3.79	3.21	0.73
CK-MB, U/L		<4	
Cardiac troponin T, ng/mL		<0.003	
Troponin I, pg/mL		<4.5	
Blood coagulation tests			
PT%, %		>100	>100
D-dimer, $\mu$ g/mL		0.8	<0.5
FDP, %			<2.5
Infection-related tests			
CMVAgC7-HRP	(-)	(-)	(-)
Stool culture test	(-)	(-)	(-)

Amy, amylase; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CMVAgC7-HRP, C7 antigenemia; Cre, creatinine; CRP, C-reactive protein; Fib, fibrinogen; Hb, hemoglobin; K, potassium; LDL, low-density lipoprotein cholesterol; Lip, lipase; LYMPH, lymphocytes; Na, sodium; NEUT, neutrophils; Plt, platelets; PT, prothrombin time; T-Bil, total bilirubin; TG, triglyceride; WBC, white blood cell;  $\gamma$ GTP,  $\gamma$ -glutamyltransferase.



**Fig. 1.** Images from abdominal X-ray examination and computed tomography scan. The X-ray film revealed intestinal gas (a), and the CT scan revealed a sigmoid volvulus (b, c). A 14-cm-long fetus was observed in the uterus (b, c).

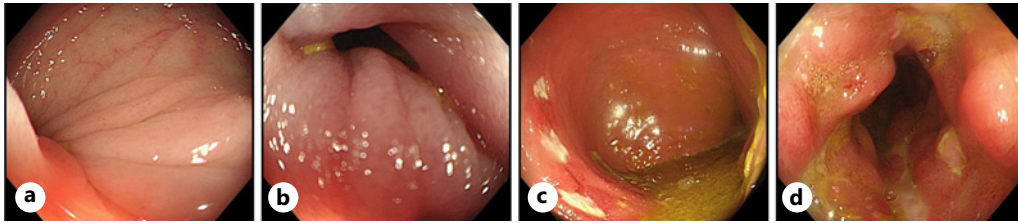
## Discussion

We described the case of a female patient with CD who underwent in vitro fertilization and became pregnant in her 40s. During pregnancy, the patient developed several complications but ultimately gave birth to a healthy baby girl by cesarean delivery.

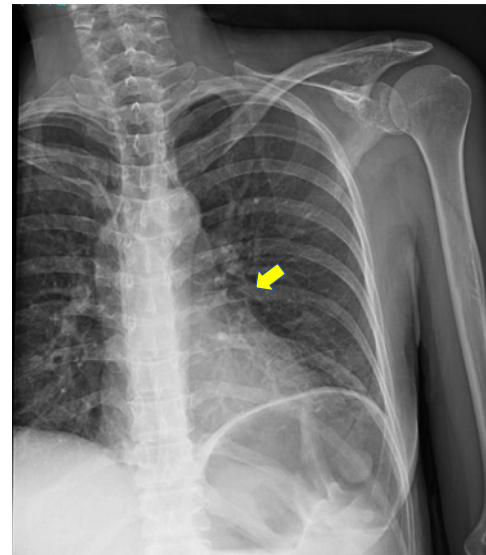
Fertility has been reported to be the same in patients with and without IBD. However, various stages of the disease and also intrapelvic surgery for IBD can affect fertility [2]. Also, women's fertility declines with aging, and aging is a risk for fetal development from conception to delivery [7]. The incidence of miscarriage starts to inversely exceed the incidence of successful pregnancy at around 40 years of age [8, 9]. The success rate of in vitro fertilization is the same in patients with and without IBD [9]. However, in patients with CD, it is necessary to control disease activity as far as possible during pregnancy and delivery.

After the present patient became pregnant, she experienced a bowel obstruction due to sigmoid volvulus. Sigmoid volvulus is rare during pregnancy, although some cases have been reported [10, 11]. It commonly occurs in late pregnancy and is related to compression by the enlarged uterus. In the present patient, sigmoid volvulus occurred at an early gestational stage and was attributed to the previous subtotal ileosigmoidostomy. In general, sigmoid volvulus should be detected and treated quickly before intestinal necrosis develops. If colon volvulus is suspected, an enhanced CT scan should be performed, even during pregnancy [12]. In the present patient, the sigmoid volvulus was quickly released by endoscopy after surgical treatment for CD was determined to be the cause. Sigmoid volvulus should be endoscopically released by a noninvasive technique as long as findings do not suggest intestinal perforation or peritonitis [13, 14]. Treatment for colon volvulus should be the same in pregnant and nonpregnant patients; however, in pregnant patients, the treatment modality should be selected by adequately considering the conditions of the pregnancy and the fetus. Treatment selection also depends on the stage of pregnancy. For patients in an early stage, as in the case of the present patient, noninvasive treatment that allows maintenance of pregnancy must be prioritized.

As for medical radiation during pregnancy, if it is 100 mGy or less, the risk is almost the same as that of normal pregnancy. A single CT scan of the pelvis exposes 25 mGy of radiation [15].



**Fig. 2.** Colonoscopy findings. **a** Stenosis was found on the anal side of the anastomosed site (**a**). The sigmoid volvulus was released under fluoroscopic guidance (**b**). Reddish edema and erosions were seen at the anastomosed site (**c**), and mucosal edema and a longitudinal ulcer (**d**) were seen on the oral side.



**Fig. 3.** Chest X-ray film. A fracture line was seen in the left seventh rib.

The patient developed thrombosis during the second trimester of pregnancy. Many cases of thrombosis have been reported in patients with CD. During pregnancy, the coagulation system is enhanced, which increases the risk of thrombosis 4- to 5-fold as compared with the risk in nonpregnant conditions [16]. Therefore, use of heparin is during the peripartum recommended for pregnant patients with IBD [17]. Treatment for CD in pregnant patients should be the same as in nonpregnant patients because pregnancy is not believed to aggravate CD. In the present patient, the colonoscopy performed in gestational week 15 to release a sigmoid volvulus revealed active pathological conditions of CD, although an assessment was difficult because the colonoscopy was not performed for screening purposes (Fig. 2).

Budesonide and GMA were used as add-on treatments. Budesonide undergoes first-pass metabolism in the liver, where about 90% of the drug is metabolized. Consequently, it has few systemic effects but acts regionally at the inflammation site, and it is recommended as a regional treatment in pregnant patients who want to avoid systemic treatment [18]. The efficacy and safety of GMA in CD have been reported elsewhere, and recommendations for the use of GMA in IBD are specified in the relevant Japanese guidelines [1]. GMA has almost no drug load, so it is considered a safe treatment, including in pregnant patients [19]. Treatment with ustekinumab was started in the present patient before pregnancy and was continued during pregnancy; it has been reported to have little influence on pregnancy and delivery [20].

Because CD is a chronic, progressive disease, relapse and aggravation must also be prevented after conception, so pharmacotherapy should be continued as far as possible under consideration of treatment benefits and risks.

In gestational week 32, the present patient suffered a rib fracture that was unrelated to external injury but was caused by fetal movement. Patients with IBD have been reported to be more prone to fracture than people without IBD, and patients with CD have a 30–40% higher risk of fracture [21]. In addition, rib fractures during pregnancy are caused by minor trauma, internal pressure, and chronic coughing, which put constant stress on the ribs from the growing uterus [22]. Her mother was underweight, had CD, had a history of long-term steroid use, and had fragile bones. It was thought that the pressure from inside the body due to strong fetal movement was added to the fracture of the ribs [23].

The reasons for the increased incidence of fracture in patients with IBD include chronic inflammation, undernutrition, and the influence of corticosteroid therapy. Pregnancy is also a risk factor for fracture because calcium loss and decreased vitamin D and estrogen levels can cause pregnancy-related osteoporosis. In particular, bone mass rapidly decreases in late pregnancy and continues to be lost during the postpartum and lactation, increasing the risk of osteoporosis. In patients with osteoporosis before pregnancy, as was the case in our patient, physicians should pay close attention to calcium levels and bone mass throughout pregnancy and during lactation. If osteoporosis develops or a fracture occurs before, during, or after pregnancy, use of artificial milk to feed neonates is recommended [24].

The mother's body is liable to undernutrition during pregnancy, and patients with CD, especially those with lesions in the small intestine and who have undergone intestinal surgery, also are liable to develop undernutrition [25]. Our patient had undernutrition due to CD, so during late pregnancy, a central venous catheter was inserted for alimentation management. However, the catheter resulted in development of sepsis in gestational week 37. Long-term catheter placement is a known risk for sepsis, and a number of cases of sepsis due to catheter infection during pregnancy have been reported [26]. Physicians should closely monitor pregnant patients in particular because catheter-related infections occur more often in pregnant patients than in nonpregnant patients. Pregnancy increases the risk of thrombosis four- to five-fold. The main reason for the increased risk of blood clots during pregnancy is increased coagulability [16].

In gestational week 38, the patient developed a second bowel obstruction, which was considered to be due to compression displacement from the pregnant uterus. Emergency cesarian delivery was performed. During the operation, no signs of volvulus were observed in the intestine. No abnormalities were apparent in the mother or her child.

The drugs used during this pregnancy had no problems with regard to teratogenicity and were continued throughout the pregnancy [3], [19, 20]. Pregnancy is generally not recommended when CD is uncontrolled [2]. However, there was a strong hope in the person, and there was a background that led to pregnancy.

## Conclusion

We described a patient with refractory CD who became pregnant and developed sigmoid volvulus, venous thrombosis, nontraumatic rib fracture, and sepsis during pregnancy. This case illustrates how the physiological changes that occur during pregnancy can cause severe complications in patients with underlying diseases such as CD, and that such patients require close monitoring and careful management.

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## Statement of Ethics

We have obtained paper consent from the patient when reporting the case. This study protocol was reviewed and approved by Tokyo Women's Medical University, number 2022-0117. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

A. Ito wrote the draft of the manuscript. Y. Maria, M. Syun, O. Teppei, S. Nakamura, and T. Katsutoshi assisted in the preparation of the manuscript. All authors have critically reviewed the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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