Case Reports in Gastroenterology

Case Rep Gastroenterol 2020;14:477–482

DOI: 10.1159/000509502
Published online: October 12, 2020

Single Case

Pregnancy-Onset Acute Severe Colitis after in vitro Fertilization Embryo Transfer

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Keywords
Pregnancy · Inflammatory bowel disease · Biologic therapy · Infliximab · In vitro fertilization

Abstract
Inflammatory bowel diseases (IBD) usually affect women in their fertile years and, therefore, have implications for their fertility and pregnancy. The presence of IBD during pregnancy has been shown to adversely affect pregnancy outcomes, and increased rates of preterm delivery and of spontaneous abortion have been reported. An onset of acute severe colitis in pregnancy has rarely been seen. We present the case of a 42-year-old woman who conceived after 9 attempts of in vitro fertilization and whose pregnancy was the result of a donated oocyte. Shortly after conception, she was diagnosed with severe active ulcerative colitis, and biologic therapy was introduced in the 28th week of pregnancy. Although therapy for IBD in pregnancy is considered safe for most drugs, this was not very well known in 2015. We also consider our case exceptional because we now have a 5-year follow-up of our patient and her child after having begun biologic therapy during late pregnancy.

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Introduction

Inflammatory bowel disease (IBD) often affects women in their peak reproductive years, and therapy is often continued during pregnancy to maintain stable disease activity. Therapeutic options have expanded over the last years, and many new drugs, especially biologics, have been introduced (golimumab, vedolizumab, ustekinumab, etc.). The majority of treatment options for IBD appears to be of low risk and may often be continued through pregnancy and lactation. It is very important for gastroenterologists and also gynecologists to understand safety data regarding the treatment options in IBD patients. The greatest risk for both mother and fetus is not treating IBD or discontinuing therapy with pregnancy [1, 2].

Case Report

A 43-year-old female patient diagnosed 1 month earlier with ulcerative proctitis was admitted to the IBD unit in April 2015 because of the increased occurrence of bloody diarrhea and abdominal pain. At admission, she was 27 weeks pregnant, and her pregnancy was the result of overall 9 attempts of in vitro fertilization. Finally, she was donated with an oocyte, and embryo transfer was successful. First, 3 months after fertilization, she received a low-dose steroid therapy.

The patient was initially diagnosed with ulcerative proctitis in March 2015, after a short history of bloody diarrhea and abdominal cramps. Native rectoscopy showed hyperemic rectal mucosa with obliterated vascular pattern up to 25 cm; further mucosa was normal. According to the Montreal classification of the extent of ulcerative colitis, it was E1. Histology was consistent with ulcerative colitis, without dysplasia and signs of activity. The patient was started on aminosalicylates topically, but her symptoms got worse and she was admitted to hospital. In her family history, her father had ulcerative colitis, and he passed away because of colonic cancer. Our patient was completely asymptomatic before pregnancy. During hospitalization, we immediately excluded cytomegalovirus and *Clostridium difficile* infection, and her control rectoscopy showed severe, active ulcerative colitis, with hyperemic, vulnerable mucosae, obliterated vascular pattern, defined as MES 2, UCEIS 3. Histology was consistent with active disease, with no dysplasia (Fig. 1). She was started on an oral steroid (prednisone) at a dose of 60 mg (her weight was around 75 kg; normal dosing is 0.75 mg/kg), but as no effect was achieved, we switched to parenteral steroid (methylprednisolone 80 mg). After a short period of improvement, her condition deteriorated and the number of bloody diarrheas increased (>6 bloody stools per day), as well as abdominal cramps, without febrile attacks. During hospitalization, she was examined on a weekly basis and monitored by a gynecologist-obstetrician. As criteria for steroid refractory were achieved, we decided to start anti-tumor necrosis factor (TNF) therapy. Our patient accepted and received her first dose of infliximab (Remicade®) at a dose of 5 mg/kg during hospitalization, as well as her second dose 7 days later, according to severe clinical state, with prompt clinical response. Her symptoms completely subsided after the initial 2 doses of infliximab. She was soon released from hospital on peroral steroid therapy (at a dose of 10 mg/day). After hospital discharge, she was controlled by a gastroenterologist and a gynecologist.

In the 38th week of pregnancy (gestational age 37+2), she was admitted to the gynecology clinic and gave birth by Caesarean section to a healthy female baby (2,330 g, 46 cm, Apgar score 9/10). Because of biologic therapy, the newborn did not receive any vaccines after birth.

After pregnancy, our patient was clinically without symptoms, with 2–3 stools per day, without blood and mucus. She received the third dose of infliximab in June 2015, and every 8 weeks after, and she continuously took aminosalicylates at a dose of 2 g per os as maintenance therapy. The first post-partial colonoscopy was performed in January 2016, 6 months after giving birth. Terminal ileum and colon were macroscopically normal, without signs of inflammation; 3 polyps in the left colon were completely removed, and random biopsies were taken from every part of the colon. Pathohistologically, all 3 polyps were marked as hyperplastic polyps, and biopsies from normal mucosa showed no signs of dysplasia but irregular crypts and lymphoplasmacytic infiltrate. After colonoscopy, the steroid was completely removed from the therapy (since giving birth, she was on 10 mg of prednisone). Therapeutic drug monitoring was performed with excellent concentrations of the drug (14.9 μg/mL), but with elevated concentration of antibodies (13.8 AU/mL). Although antibody concentration was neither too high nor worrying with regard to high drug concentration, azathioprine at a reduced dose, despite normal thiopurine-methyltransferase enzyme (genotype *1*1), was introduced as a therapy in June 2016. But because of the patient's concerns about azathioprine side effects, the drug was stopped in October 2016. Fecal calprotectin in the control period was always <20 μg/g. Two more colonoscopies were performed from January 2017 to December 2018. Both were total colonoscopies, and both showed no inflammation, histologically with chronic inflammation but without dysplasia (Fig. 2). Fecal calprotectin was always <30 μg/g. As our patient had been in complete remission for almost 3 years, she was discussed in our IBD team, and the decision was to try stopping biologic therapy, so her last dose of infliximab was administered in February 2018.

Since then, she has been in complete remission with no clinical symptoms, with normal laboratory findings and normal fecal calprotectin, only taking aminosalicylates at a maintenance dose of 2 g.

Her baby girl, who was conceived with a donated oocyte, is a healthy 5-year-old child.

Discussion

When our patient started biologic therapy, it was still considered relatively new, and short- and long-term effects were still elucidated. However, given clinical experience at the time, we knew that these medications were generally compatible with use during pregnancy, which was very important, as there were data to suggest that women with IBD were at increased risk of fetal loss, preterm delivery, low birth weight, and other adverse pregnancy outcomes, particularly if they had active disease at conception or during pregnancy. The Food and Drug Administration (FDA) classified infliximab, adalimumab, and golimumab in category B, which meant that they did not demonstrate a fetal risk [3, 4]. Since then, many studies have come to the same conclusion about managing IBD therapies in pregnancy: aminosalicylates, antibiotics, and steroids are all of relatively low risk for use during pregnancy and breastfeeding, but recent studies have also supported the safety of continuing immunomodulators and anti-TNF agents during pregnancy and while breastfeeding [4].

Infliximab is a chimeric monoclonal antibody directed against TNF-α, used in the induction and maintenance of remission in Crohn's disease and ulcerative colitis. Infliximab was the first biologic to be approved for treating IBD during pregnancy, and multiple studies reassuring its safety for use in pregnant women have been completed [5]. It is an IgG1 antibody which can cross the placenta, particularly in the second and third trimesters. There is growing evidence that infliximab exposure is of low risk in pregnancy, at least for the early outcomes,

including the absence of teratogenic effects. The preliminary data from the PIANO study also suggest that the use of anti-TNF agents is safe during pregnancy: no differences in the rate of congenital malformations and other short-term adverse pregnancy outcomes were found between the pregnancies exposed to thiopurines or anti-TNF monotherapy and the control group [6]. The mode of delivery should primarily be dictated by obstetric necessity.

Cesarean section is recommended in patients with perianal disease or in case of active disease with rectal involvement [6]. Each decision should be individualized based on the distinct characteristics of the patient and her disease. Fetal exposure to most IBD medications is considered to be of low risk to the child, except for methotrexate and thalidomide that are contraindicated due to teratogenicity. The risk of infection with anti-TNF agents alone or in combination with immunomodulators is controversial. The active transport across the placenta of these monoclonal antibodies occurs during the third trimester of pregnancy [4]. Since detectable levels of anti-TNF in the offspring are present in the first 6 months at least, live vaccines should be avoided in this period [6]. The previous recommendations were to avoid giving oral polio virus and Bacille Calmette Guérin (BCG) vaccines during the first 6 months of life, but this may need to be extended to the first 12 months or until the anti-TNF drug levels are no longer detectable. Also, timing of the last dose of infliximab should be as late in the second trimester as possible to maintain remission but to limit the transport of the drug to the fetus.

Another point to mention in this case report is the onset of severe ulcerative colitis in the previously healthy woman. We can only suppose that genetic factors (her father was diagnosed with ulcerative colitis and died of colorectal carcinoma), the fact that she stopped smoking before conception, or plentiful hormonal therapy while on in vitro fertilization have led to the onset of ulcerative colitis. This shows the importance of taking the history of patients, knowing possible genetic connections and lifestyle changes that can lead to the appearance of symptoms and disease.

This case report reveals that the treatment with anti-TNF-α in a late pregnancy of an IBD patient improved the patient's symptoms and saved her and her fetus. In 2015, when our patient was hospitalized with severe acute colitis, it was not usual to start biologic therapy, particularly in the third trimester. The guidelines we had back then mentioned introducing biologic therapy in cases of severe fetal danger or high possibility of colectomy. Obviously, colectomy in our patient with severe steroid-refractory colitis in the 28th week of risk pregnancy was not an optimal solution, and we decided in our team, consisting of a gastroenterologist, an obstetrician, and a surgeon, to start biologic therapy with infliximab. All the time, our patient remained on a low dose of steroid (prednisone 10 mg) in order to prevent production of antibodies to infliximab, as azathioprine was not supposed to be started in pregnancy. We found that infliximab therapy in late complicated pregnancy was safe for both the mother and the fetus.

Almost 5 years since giving birth, we are now sure that biologic therapy with infliximab is safe both for women and children. It is once more important to stress the necessity of controlling disease activity throughout pregnancy.

Statement of Ethics

This study is a case report and the patient agreed that this case is described and published, although her identity is never mentioned.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

No funding was used for this manuscript.

Author Contributions

Dora Grgić: conceptualization of design, investigation, writing original draft. Silvija Čuković Čavka: conceptualization, investigation, revising. Vesna Elveđi Gašparović: data curation, formal analysis, drafting. Nikša Turk: investigation, methodology, visualization. Marko Brinar: methodology, visualization. Zlatko Marušić: investigation, methodology, drafting. Željko Krznarić: supervision.

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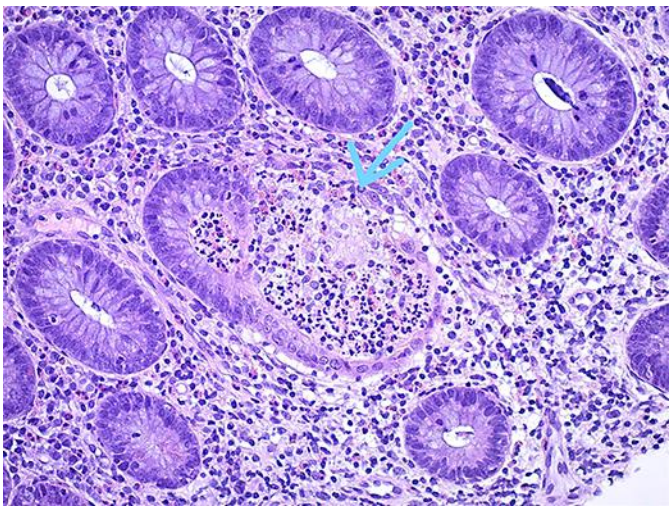

Fig. 1. Active-disease crypt abscess with crypt rupture (HE, ×200).

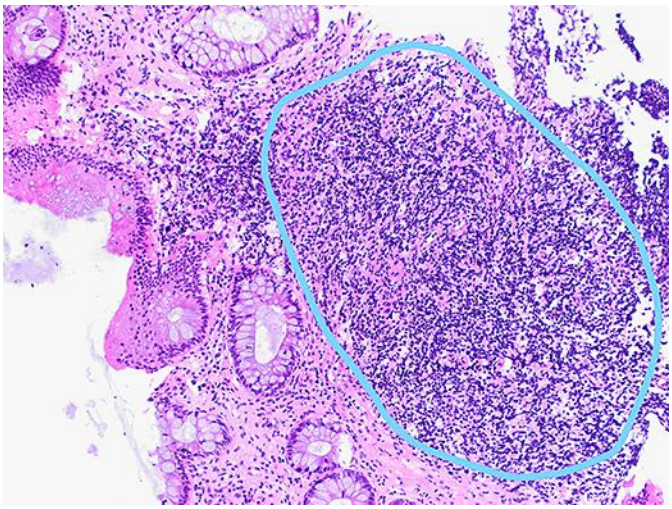

Fig. 2. Remission of chronic inflammation (HE, ×100).