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A special combination of pregnancy and inflammatory bowel disease: case report and literature review

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Abstract

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract. Onset typical occurs in adulthood. Its incidence is increasing everywhere, the highest incidence of Crohn's disease of 20.2 per 100,000 people/year is in North America while the incidence of ulcerative colitis is 24.3 per 100,000 people/year in Europe. Since it is not curable, the remission is the main objective of management. Many women are affected by IBD at different stages of their lives, including during reproductive life, pregnancy and menopause, so the way the disease is managed in reproductive age women can affect IBD's course. Treatment and maintenance strategies are very relevant. For patients with a desire to have children, disease remission is very important from conception through pregnancy to birth to ensure adequate results for both mother and fetus. It is well known that active disease during conception and pregnancy is associated with adverse outcomes of pregnancy. In addition, active perianal disease is an indication for cesarean delivery which entails increased risk of bowel surgery and complications in the postoperative period. We present a case of IBD during pregnancy.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, pregnancy.

The patient was a 32-year-old woman with chronic diarrhea containing mucus and blood that was associated with intermittent colic. She had shown some improvement after treatment with multiple antibiotics. Two years prior to onset, a pregnancy had ended at 26 weeks with a stillbirth. Following the miscarriage, her gastrointestinal symptoms worsened. Fetal malformations found included overgrowth of limbs, hemifacial microsomy and hydrops. A colonoscopy found severe ulcerative colitis (UC) compromising the left colon. I inflammatory bowel disease (IBD) was diagnosed. Oral administration of 40 mg/day of steroids and 4 g/day of mesalazine was begun. The patient's clinical condition improved, but she continued to lactate. Her condition was determined to be a corticodependent disease and biological therapy with infliximab and 2.5 mg/kg/day of azathioprine was begun.

The patient developed a severe infectious process which required suspension of biological therapy. Management with azathioprine and mesalazine continued. At the age of 37 years, she was hospitalized again with severe exacerbation of both clinical and endoscopic disease triggered by poor adherence to the established treatment. She again required steroids, but due to corticosteroid criteria it was decided to restart infliximab and to continue azathioprine and mesalazine. Good control of the disease was achieved. The patient then consulted with a pregnancy of 5 weeks. She was told to continue biological therapy, but thiopurine was suspended. Despite medical advice, the patient decided to suspend all types of medication. The pregnancy proceeded normally, without any complications. She delivered a live fetus with low birth weight but without other complications by caesarean section. During the first ten

days postpartum, the patient' intestinal disease worsened. Mesalazine was begun again but she decided not to restart biological therapy despite the medical recommendation.

This case demonstrates the impact of IBD on gestation and postpartum health. In clinical practice, the management of this type of patient is a challenge for the gastroenterologist and gynecologist. Multiple questions arise when these two entities are both present. We will try to answer these questions below.

WHAT IS THE NORMAL IMMUNOLOGICAL RESPONSE DURING PREGNANCY?

Naïve T helper cells ($CD4^+$) differentiate into Th1 and Th2 depending on the type of cytokines most prevalent in the environment in which they are produced. If IL-12 and TNF prevail, differentiation to Th1 is favored, but if IL-4 predominates differentiation to Th2 is favored. Th1 cells induce various cytotoxic and inflammatory actions mediated by the action of IL-2, IL-12, INFγ, and TNFα, and are responsible for inflammatory reactions of cellular immunity, delayed hypersensitivity, and tissue damage in infectious diseases. and autoimmune. Th2 cells produce IL4, IL5, IL6 and IL10 and are associated with a humoral-type responses which favor the appearance of antibodies. (1)

In addition, there are cytokines that do not match the typical Th1 and Th2 responses but which are important for maintaining pregnancy. They include IL-11 and IL-18 which are present at specific times of pregnancy suggesting regulatory functions. (1) A prevalence of Th1 response over Th2 response has been found to be associated with higher rates of fetal resorption, implantation failure, INFγ production, and lower resistance to infection. (2) Direct cytotoxic action of Th1 response on embryos has been demonstrated to cause trophoblastic cell lesions. Both TNFα and INFγ inhibit trophoblastic growth in vitro, and cytokines associated with Th2 responses contribute to embryo implantation, development of the placenta and survival of the fetus until the end of gestation. (3)

Different cytokines are produced in different amounts depending on the time during gestation at which they are assessed as well as on their receptors. Both inflammatory and anti-inflammatory cytokines are expressed in maternal peripheral blood. They include IL-2, IL-4, IL-10, and INFγ, so appears that the maternal immune system is not compromised during pregnancy as had been thought previously. (4)

Production at the maternal-fetal interface depends not only on the relatively few CD4 T lymphocytes, but also on other cytokine-producing cells in maternal and fetal territories. Thus, the trophoblast, macrophages within the villous trophoblast, NK cells, and macrophages and stromal cells in the decidua contribute to maintaining the Th2 environment which develops during the first trimester of gestation. Towards the end of the third trimester as the mother's body prepares for labor, a shift to Th1 predominance occurs. This has led some authors to see these immunological phenomena as elements in the mechanisms that initiate labor.

Although data is not conclusive, hormones, especially estradiol, progesterone, the placental pregnancy-specific protein (SP-1), and plasma protein associated with pregnancy (PAPP-A), appear to have roles in immunomodulation during pregnancy. SP-1 stimulates the production of Th2 cytokines by monocytes, PAPP-A inhibits in in vitro T-cell proliferation while secretion of IL-2 contributes to maternal tolerance by promoting the Th2 response over Th1.

Leukocyte inhibitory factor (LIF) is synthesized and secreted by the maternal endometrium and stromal cells. Its receptor is necessary for implantation, differentiation and growth of the trophoblast. (1) Among the substances that activate LIF are progesterone, IL-4 and IL-1. INFγ and IL-12 inhibit it.

Progesterone production by the corpus luteum, necessary for maintenance of pregnancy, is stimulated by IL-6 and IL-4. The lymphocytes of pregnant women are especially sensitive to progesterone. Pregnancy increases the number of progesterone receptors that are exposed in peripheral blood lymphocytes. This makes them more susceptible to progesterone inhibitory mechanisms. In their presence, lymphocytes secrete a protein that directly inhibits the cytolytic effect of NK. Progesterone concentrations only suppress the immune system locally within the uterus and placenta. (1)

Progesterone in the syncytiotrophoblast favors production of Th2 cytokines. Progesterone, catecholamines, prostaglandins and human chorionic gonadotropin induce the production of IL-10. Estrogens cause the endometrium to produce chemotactic interleukins and macrophages which are attracted to the maternal-fetal interface. (5) Taking all of this into account, a Th2-type immune response predominates in pregnancy and could be related to the type of response to IBD.

A study evaluating the types of cytokines in the different kinds of IBD has shown that ulcerative colitis tends to have higher levels of IL5 production which leads to a predominance of Th2 response. This could exacerbate the disease during the establishment of pregnancy.

WHAT IS THE EFFECT OF INFLAMMATORY BOWEL DISEASE ON FERTILITY?

Inflammatory bowel diseases occur between the ages of 33.4 and 45 years, and it is vitally important to understand that infertility rates in women with inflammatory bowel

disease without activity are similar to those of the general population (8% to 10%). (6) Remission of the disease not only improves fertility rates, but most studies have also shown that it leads to more favorable pregnancy outcomes. Active disease reduces fertility, probably in response to the inflammatory process and adhesions that develop in the fallopian tubes and/or ovaries.

Similarly, patients who have previously had surgery such as a proctocolectomy or ileal anastomosis with an anal reservoir have 3 to 4 times greater risks of infertility. This is due to the pelvic adhesions that tend to form and which affect the permeability of the fallopian tubes leading to obstructions. (7) Therefore, the recommended time for conception is 3 to 6 months following remission of the disease.

There is no evidence that inactive ulcerative colitis or Crohn's disease (CD) affects fertility, but decreased fertility among patients with ileal bags has been documented.

WHAT IS THE EFFECT OF INFLAMMATORY BOWEL DISEASE ON PREGNANCY?

Patients with CD or UC have worse pregnancy outcomes than do healthy women. Studies have also shown that the odds of worse pregnancy outcomes are greater in patients with Crohn's disease than in patients with ulcerative colitis.

A 1998 review by Subhani et al. found that Crohn's disease, especially when active, is associated with decreased birth weight, premature delivery, and cesarean sections. (8) Furthermore, patients with IBD have labor induced more frequently than women who do not have IBD (32% vs. 24%, $p = 0.002$), undergo caesarean sections more frequently (32% vs. 22%), and develop chorioamnionitis more frequently (7% vs. 3%, $p = 0.04$). Rates of occurrence of neonatal complications including low birth weights, intrauterine growth restrictions, Apgar scores and congenital anomalies were found to be similar in populations with and without IBD. (9) There are no studies reporting greater probability of fetal malformation in these patients which makes this case striking. Although there may be multiple factors associated with fetal malformation, it is noteworthy that fetal death ending the first pregnancy was related to the onset of the inflammatory disease and presentation of the morphological alterations described. This invites reflection on this topic. Despite the absence of clear evidence in this regard, prenatal follow-up of these patients should be especially detailed and strict.

Another study of 461 pregnant patients with IBD showed that patients with IBD were at increased risk of miscarriage, eclampsia, preeclampsia, placenta previa, premature placental abruption, and premature rupturing of membranes. That study did not find that active disease was associated with worse outcomes, but did find that diagnosis of IBD, a history of IBD bowel surgery, and not being white were independent predictors of worse outcomes. (10) These results support current treatment guidelines which indicate that maintaining remission during pregnancy is of vital importance. It is important to understand that the risks faced by this type of patient can be reduced to those of the general population if disease is controlled at the beginning of gestation.

WHAT IS THE EFFECT OF PREGNANCY ON INFLAMMATORY BOWEL DISEASE?

Approximately 80% of women with IBD who become pregnant when the disease is in remission tend to remain in remission throughout pregnancy and the postpartum period. About 66% of patients who have active disease at conception continue to have active disease or worsening disease during pregnancy. (11) Ulcerative colitis worsens during the pregnancies of up to 45% of patients who have diagnoses of active ulcerative colitis when they conceive. Crohn's disease worsens in 30% of the patients who conceive while their disease is active. (12)

A prospective study has found that the disease exacerbation rate in pregnant of pregnant Crohn's disease patients in remission were similar to the disease exacerbation rate in Crohn's disease patients who were not pregnant. (3) On the other hand, relapse rates were higher among women with Crohn's disease who conceived while their disease was active than among non-pregnant patients with Crohn's disease (50% vs. 33%, respectively). Pregnant patients with ulcerative colitis had a higher risk of exacerbation of the disease during pregnancy and in the postpartum period than did controls. Exacerbation of the disease was most frequent in the first six months of pregnancy and in the first three months of the postpartum period. (13) This should make it clear that active disease at the time of conception helps predict the course of the disease during pregnancy. Ideally, women should be in remission at the time of conception.

HOW DO MEDICINES USED TO MANAGE INFLAMMATORY BOWEL DISEASE AFFECT FERTILITY?

Although there are no data on the effects of IBD medications on female fertility, it is clear that immunosuppressants such as methotrexate have clear associations with teratogenicity and are totally contraindicated in patients who have a desire to conceive.

The use of sulfasalazine has been reported to condition reversible reduction of sperm motility, an effect related to drug dosage. (14) Methotrexate favors oligospermia which

may improve over time when use of the drug is stopped. (15) Infliximab appears to affect semen quality by reducing sperm motility. (16) Azathioprine has not been found to influence sperm quality. (17)

WHAT SIDE EFFECTS DO MEDICINES HAVE FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN PREGNANCY?

IBD management guidelines recommend that pregnant women who need pharmacological treatment to maintain remission of the disease should continue to use those medications during pregnancy. However, methotrexate must be discontinued prior to conception and during pregnancy. In addition, any exacerbation of disease during pregnancy should be treated aggressively.

Although the FDA's risk category classification for pregnancy is no longer widely used we have used them in the descriptions below of medications that are frequently used in pregnant patients with IBD.

Aminosalicylates and sulfasalazine (class B)

In general aminosalicylates and sulfasalazine (class B) are considered to be insurance. A cohort study conducted in Denmark found increased risk of preterm birth and stillbirth in women who received aminosalicylates during pregnancy. However, that study made no distinction between the effects of disease activity and the use of aminosalicylates. (18) Other studies have not found any significant association between aminosalicylates and adverse effects during pregnancy. (19)

Women who use sulfasalazine, which is known to inhibit synthesis of folates, must take folic acid supplements to reduce adverse effects on the neural tube. (20)

In summary, aminosalicylates and sulfasalazine can be used without limitation during pregnancy and are not associated with significant adverse outcomes.

Thiopurine (azathioprine) (class D)

It has been shown that fetal serum levels of thiopurine can reach levels as high as 5% of the maternal drug level. Results of human studies regarding the safety of using azathioprine during pregnancy have been discordant, but it is recommended that this drug be continued during pregnancy in order to maintain the disease in remission. Recent studies have shown that the use of azathioprine does not favor increased risk for the fetus and that it is safe to continue the medication during pregnancy considering that tradeoff between the negative impact of active disease and the uncertain effects of the medication. (21)

Methotrexate (class X)

It is well known that methotrexate has teratogenic and abortifacient effects, so it is contraindicated during conception and pregnancy. The use of methotrexate between the sixth and eighth week of pregnancy can favor congenital anomalies while use in the second and third trimester favors miscarriages. In addition, methotrexate should be suspended three to six months before attempting conception since it actively persists in body tissues. (20)

Corticosteroids (class C)

Glucocorticoids are known to cross the placenta and can reach the fetus, but enzymes of the placenta convert corticosteroids into less active metabolites. These types of medications are frequently used to treat episodes of inflammatory bowel disease activity. Contradictory results are found in pregnancy, but there are reports of increased numbers of orofacial fissures in newborns when they are used in the first trimester of pregnancy. (22)

There are few data regarding the exact dosages of corticosteroids that induces toxicity in either the mother or the fetus. They should be administered with caution and at the discretion of the treating physician. Studies of in other autoimmune diseases have been extrapolated to show that corticosteroids favor preterm deliveries and low birth weights.

Antibiotics

Metronidazole (class B) and ciprofloxacin (class C) are frequently used to treat abscesses and fistulas in IBD patients. They are detectable drugs in breast milk at low levels. A study of women with IBD who required metronidazole during pregnancy has found it to be safe in all trimesters, but recommended avoidance of its use in the first trimester. (23) Studies of ciprofloxacin have not reported any significant increases in major congenital abnormalities including musculoskeletal problems, but it is recommended that it not be used during pregnancy given the risk of congenital arthropathy. (24)

Penicillins have not been shown to condition fetal malformations or adverse pregnancy outcomes and are considered to be first line therapy in pregnancy.

Cyclosporine (class C)

Cyclosporine crosses the placenta but does not cause teratogenicity in animal models. Studies conducted with this drug have been related to kidney transplantation, so an association with low birth weight and preterm delivery is suggested. Similarly, in severe relapses of ulcerative coli-

tis during pregnancy, cyclosporine has been used with favorable responses because it has reduced the need for colectomies without significant adverse effects. The most frequently reported side effect is hypertrichosis in the mother. Other adverse effects that have been described include nephrotoxicity and hepatotoxicity. (25) The use of cyclosporine can be considered in patients with fulminant ulcerative colitis during pregnancy.

Biological agents (class B)

Anti-TNFs such as infliximab, adalimumab, certolizumab, and golimumab are biological agents that are used to manage moderate to severe inflammatory bowel disease and fistulizing-stenosing Crohn's disease. Since TNF is mainly produced by the placenta, levels increase during pregnancy. TNF is important in the early stages of pregnancy and is also important for the development of the fetal immune system.

Observational studies and systematic reviews have shown their safety during pregnancy, but both infliximab and adalimumab are IgG1 monoclonal antibodies that cross the placenta while Certolizumab is a Fab fragment of IgG1 which does not cross the placenta. (26) For this reason, infliximab and adalimumab are not recommended from the second trimester of pregnancy. (27) Other groups have recommended continuation of biological therapy throughout pregnancy, especially in high-risk patients with active disease activity. They only recommend suspension when requested by the pregnant woman. (28) When suspension of biological therapy to decrease fetal exposure is considered, it is recommended that administration cease between the 22nd and 26th week of gestation.

Increased rates of miscarriage, stillbirth, birth defects, and preterm births have not been observed among pregnant women who have been exposed to adalimumab or golimumab. Also, anti-TNFs do not have higher risks of complications during pregnancy than does thiopurine or suspension of all medications. (29)

Levels of infliximab and adalimumab have been detected in infants up to 12 months after delivery, but no increases in infections or allergic reactions have been detected nor have decreased responses to vaccines been found. Nevertheless, it has been observed that infants exposed to the combination of immunomodulators and biological agents have more infections than other infants between 9 and 12 months of age. (30)

Anti-integrin (class C)

Anti-integrin is a humanized monoclonal IgG4 antibody that acts against the α4-integrin adhesion molecule. Data are scarce regarding its use during pregnancy. A review of the natalizumab global safety database did not find increased rates of birth defects among children whose mothers were exposed to natalizumab during pregnancy. It is possible to extrapolate to other diseases from the results of the pregnancies of 35 multiple sclerosis patients who accidentally became pregnant while being treated with natalizumab. Of these patients, 29 had viable pregnancies, 28 had unchanged children, and 1 child was born with hexadactyly. Of the remaining six patients, one decided to undergo an abortion and the other five miscarried. (31)

WHAT IS LABOR LIKE IN WOMEN WITH INFLAMMATORY BOWEL DISEASE?

In the context of pregnancy and IBD, labor should be managed by a multidisciplinary team including an obstetrician, a gastroenterologist and a coloproctologist. Cesarean delivery is indicated when the patient has active perianal disease, rectovaginal compromise, or a surgical history of ileoanal reservoir or ileorectal anastomosis secondary to IBD. Vaginal delivery with episiotomy has been shown to be related to increased risk of perianal damage. (32) Vaginal delivery with all of its benefits for a newborn is indicated for IBD patients who have no perianal compromises. Studies suggest that cesarean delivery is a risk factor for the development and exacerbation of IBD.

WHAT SHOULD WE TAKE INTO ACCOUNT DURING BREASTFEEDING?

Breastfeeding may be associated with increased inflammation since prolactin is associated with increased production of tumor necrosis factor. Nevertheless, one study found that the rates of disease relapse in the first postpartum year were similar among women who breastfed (26%) and those who did not (29.4%). (33)

The following guidelines regarding the use of medications during lactation should be taken into account:

- Aminosalicylates and sulfasalazine can be continued during lactation, bearing in mind that aminosalicylates can favor osmotic diarrhea and sulfasalazine can cause jaundice. Nevertheless, drug concentrations in breast milk are low.
- Azathioprine can be continued during lactation. It is detected in low concentrations in breast milk, although higher concentrations of the drug are found during the first 4 hours after consumption of the drug. It is recommended that milk obtained during these hours be discarded.
- Methotrexate is contraindicated during lactation because of its teratogenic potential.

- Corticosteroids are found in low concentrations in breast milk, with moderately high levels being found in the first 4 hours after taking the drug. It is recommended that milk obtained during these hours be discarded.
- Biological agents can be continued during pregnancy. Minimal concentrations of infliximab and adalimumab are found in breast milk and no significant adverse events have been reported in infants. Detectable levels in newborns are related to placental transfer.. In addition, no association has been found between breastfeeding and the risk of infection in newborns exposed to biological agents. (34)

Vaccination with non-living viruses in newborns exposed to anti-TNF in the womb does not differ from unexposed babies, so they have adequate responses to vaccination. Vaccines with live viruses such as rotavirus, oral polio and BCG should be provided only when anti-TNF levels are no longer detectable. Babies should not receive live vaccines during the first 6 months of life, and anti-TNF should be suspended at week 33 of pregnancy although some other authors suggest it should be suspended at week 26. Suspension allows delivery to occur with undetectable levels of it thus eliminating its involvement in the newborn's vaccination schedule.

CONCLUSION

The medical team for patients with IBD must clearly understand how to face manage preconception, conception and postpartum for these patients since multiple factors must be taken into account. These include disease control during fertility, pregnancy management, and clarity about the use of medications during the various stages of a woman's pregnancy and postpartum period. This will provide peace of mind for both the treating doctor and the patient. Appropriate education and awareness increases the probability that physicians will follow best practice guidelines for management of pregnant patients with IBD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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