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General review on pregnancy in inflammatory bowel disease

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ABSTRACT

Given the age of highest incidence rate of inflammatory bowel disease, aspects such as fertility and pregnancy are especially relevant in the management of these patients. This review article aims to provide a summarized description of the basic concepts that the gastroenterologist should know when examining a patient with IBD with reproductive intentions and/or pregnant. The review as conducted selected the most recent and relevant articles on these topics and provides updated information on the latest treatments currently available.

Keywords: Pregnancy. Fertility. IBD. Activity. Risk. Malformations.

INTRODUCTION

The rate of inflammatory bowel diseases (IBD) —Crohn's disease (CD) and ulcerative colitis (UC)— has gone up over the past decade becoming a global disease. The median age of diagnosis of UC and CD is 35 and 30 years, respectively. In women, this age range includes the reproductive years and has implications on their fertility, pregnancy, and IBD treatment (1). Caring for pregnant women with IBD can be challenging, requires a multidisciplinary care team, and should always be

individualized.

This review summarizes the key management aspects of IBD treatments during conception, pregnancy, and newborn phases (Table 1).

RELATIONSHIP BETWEEN IBD AND FERTILITY

Fertility in women with IBD essentially depends on the activity of disease itself. Patients with quiescent IBD have similar fertility rates compared to the general population. There is no evidence that medical treatment affects fertility in women (2). However, patients with IBD usually have fewer children compared to the general population. The patient's choice is the main reason. Many can be the contributing factors: fear of intimacy and disease transmission, lack of disease knowledge, and fear of fetal complications associated with treatment, among others. This suggests that these patients may benefit from increased education on their disease, and pregnancy (3-5).

In addition, active CD can decrease female fertility directly by inducing inflammation in the fallopian tubes and ovaries and perianal disease-induced dyspareunia; and indirectly through surgical procedures associated with tubal adhesions. Ovarian reserve, an indicator of fertility in females of reproductive age, is also impaired due to lower serum Anti-Müllerian Hormone (AMH) levels (6). On the other hand, in active UC, pelvic surgery is the main risk factor decreasing fertility due to scarring, adhesion or damage to reproductive organs. Therefore, it is essential to strongly consider all potentially therapies in young women of reproductive age with severe UC before committing to colectomy. When surgery is needed, open pelvic surgery offers worse results on fertility rates. A huge meta-analysis has confirmed this fact showing a 3-fold increased risk of infertility in these patients (7).

There are conflicting studies on the success rate of assisted reproductive therapy (ART) in patients with IBD and infertility. Some studies describe lower rates compared to those from the general population while others describe just the opposite. There seems to be a consensus on the fact that the efficacy rate of ART is lower in patients with previous surgery to treat their disease (8,9).

PLANNING FOR PREGNANCY

Family planning for all women with IBD should include consultation with their gynecologist and gastroenterologist. Three to 6-month remissions before conception reduce the risk of flare-ups during pregnancy and the postpartum period. When pregnancy occurs when the disease is active the frequency of mother and fetus-related adverse outcomes increases parallel to a higher rate of preterm birth, low birthweight, thromboembolic events, and emergency cesarean delivery. Therefore, conception should be planned and take place during disease remission. Besides, optimization of preconception nutritional status and smoking cessation are essential.

MEDICAL MANAGEMENT OF IBD DURING PREGNANCY

Management of pregnant patients with IBD requires a multidisciplinary team including gastroenterologists, colorectal surgeons, obstetricians, and obstetric anesthesiologists. The transfer of this kind of patients to a tertiary center —preferably one affiliated with a high-risk obstetrics program— is advised (10).

Monitoring disease activity throughout pregnancy is imperative. Patients should be examined, at least, once per trimester by their gastroenterologist, and more regularly in the presence of active disease. Serial assessment of fecal calprotectin and serum markers including hemoglobin, albumin, C-reactive protein should be conducted before conception and each trimester including physiological changes during pregnancy like elevated C-reactive protein levels, mild dilutional anemia, and low albumin levels.

Exposure to radiation should be avoided, and imaging should be acquired through intestinal ultrasound and magnetic resonance imaging modalities without gadolinium during the second and third trimesters (11).

Endoscopy during pregnancy

Limited evidence exists on the utility and safety of endoscopy in patients with IBD during pregnancy so further studies are needed. Gastroscopy, sigmoidoscopy, colonoscopy, and ERCP are generally considered safe during pregnancy. They should be spared for strong indications and preferably during the second trimester.

The most important considerations to make are the increased risk of aspiration following gastroscopy and the adequate maternal oxygenation to ensure optimal placental perfusion. The presence of a specialist in obstetric anesthesia is essential. Oxygen monitorization is indicated. Pregnant patients should be placed in the left pelvic tilt or left lateral position during the endoscopic procedure to avoid compressing the vena cava. Sedative drugs should be administered to provide patient comfort, but they should be used at the lowest possible dose. Fentanyl is commonly administered and considered safe. Benzodiazepines should be avoided, especially within the first trimester.

Special considerations to make with ERCP are the highest risk of acute pancreatitis and use of the minimum dose of radiation (12).

Medical treatment during pregnancy

All discussions on medication during pregnancy are based on best available data considering the risk of maternal disease flare-ups, and aware that the long-term follow-up of these children is not available. The balance of minimizing both medication toxicity and active disease should be explained to patients. Fortunately, most drugs used to treat IBD are thought to be safe for use during pregnancy.

Drugs

5-aminosalicylates

5-aminosalicylic acid derivatives in pregnant women reach only low levels in fetal circulation due to poor transplacental transfer and rapid renal excretion. Their use is considered to be safe during pregnancy, and they can be maintained (13). Sulfasalazine crosses the placenta and inhibits the absorption and metabolism of folic acid. It, however, has not been associated with teratogenic or embryogenic effects. It is thought to be safe during pregnancy in combination with high supplementary doses of folic acid (2 g/day) during conception and pregnancy to prevent neural tube defects (10).

Corticosteroids

All corticosteroids can cross the placenta into the fetus, but they are rapidly converted into fewer active metabolites. Prednisolone does not cross the placenta as effectively as other steroid formulations so it should be considered the first-line therapy if corticosteroid treatment is required.

Corticosteroids are associated with a higher risk of orofacial malformations (cleft lip/palate) when administered within the first trimester, and with neonatal adrenal suppression when administered within the late pregnancy phase. They can also be associated with maternal complications such as hypertension, diabetes, and preeclampsia. To reduce risks the lowest dose and shortest duration is advised (14).

Immunomodulators

- *Thiopurines*. The use of thiopurines during pregnancy has been associated with an increased risk of congenital abnormalities in animal studies but it is thought to be safe in humans. As a matter of fact, most recent studies have not shown any increase in congenital malformations or immunological abnormalities following thiopurine exposure in utero and they appear to be safe for use throughout pregnancy (15).
- *Cyclosporine*. Evidence on the use of cyclosporine to treat IBD is limited to small series of women in severe relapse during pregnancy. No genetic malformations were described but the rates of prematurity and low birthweight were higher being the impact of severe disease difficult to differentiate from the effect of the drug.
- *Methotrexate*. Methotrexate is contraindicated during pregnancy because of its teratogen effect and should not be prescribed to women contemplating pregnancy or unwilling to use reliable contraception. It should be stopped at least 3 to 6 months prior to attempting conception and a high dose of folic acid should be administered (16). If a woman becomes pregnant while taking methotrexate, the medication should be immediately stopped, folic acid supplementation started, and she should be referred to an obstetrician to discuss the risk of teratogenicity.

Biological agents

Anti-TNF agents: infliximab, adalimumab, golimumab, and certolizumab

Anti-TNF agents are IgG1 antibodies. They are large molecules (> 100 kDa) that can only cross the placenta through active transportation, joining the maternal placenta Fc receptors. Certolizumab, which has only been approved for the management of CD, does not contain the Fc portion of the mAb, making it the preferred option for women who start using anti-TNF agents during pregnancy. Its levels in cord blood remain undetectable (17). Cord blood levels inversely correlate with the time elapsed since the last drug administration and are significantly higher for infliximab compared to adalimumab when both ceased at similar gestation weeks.

Patients with anti-TNF therapy usually have a history of moderate-to-severe disease. Maintaining remission in this group of patients is really important to avoid complications. In pregnant women with IBD on anti-TNF maintenance therapy, continuation therapy is recommended (18). In a selected group of women with low risk of flare-ups (those who are in remission), anti-TNF therapy can be discontinued at the 20th (infliximab) and 24th weeks (adalimumab) of pregnancy to minimize fetus exposition and potential immunosuppression of the newborn baby.

Special considerations about vaccination should be made for newborn babies of women on anti-TNF therapy while live vaccines should be avoided for 6 to 12 months (19).

Although these data are reassuring regarding anti-TNF monotherapy, the effect of combination therapy with thiopurines is less clear. Several studies found no increased risk of childhood infection, maternal or fetal adverse effects associated with the combination therapy (18,20,21).

Anti-integrin agents: vedolizumab

Safety data for vedolizumab use in pregnancy is still limited but major adverse effects have not been reported. The frequency of congenital abnormalities was similar between vedolizumab and anti-TNF groups. The rate of infection within the first year

of the baby's life is also similar compared to other biological agents. Due to the expected safety of vedolizumab during pregnancy, the last dose of vedolizumab should be planned 8 weeks before delivery (22). Same as for anti-TNF agents, live vaccines should be avoided for up to 1 year in children exposed to vedolizumab.

Anti-IL12/23: ustekinumab

Further studies on the safety profile of ustekinumab during pregnancy should be conducted (18). The most important societies of rheumatology and dermatology consider ustekinumab a safe medication during pregnancy. However, doses used for IBD are usually higher compared to those used to treat psoriasis or rheumatoid arthritis so these results may not necessarily extrapolate to patients with IBD. If ustekinumab is maintained during pregnancy, it is reasonable to assume that transplacental passage will be similar to that of anti-TNF agents (IgG1) while concentration during organogenesis stage is minimal. Overall, ustekinumab is likely to be safe for use during pregnancy. However, further data is still needed (23).

Oral janus kinase inhibitors

As a small molecule, tofacitinib is likely to cross the placental barrier; however, information on its effects on pregnancy outcomes is limited. It has been associated with fetocidal and teratogenic effects in animals. Therefore, it should be avoided during conception and pregnancy. In fact, European recommendations are to use effective contraception between 4 and 6 weeks after the last dose (8).

Antibiotics

Ciprofloxacin, and metronidazole, the most used antibiotics in IBD, should be avoided beyond the first trimester of pregnancy on concerns about its effects on organogenesis. Amoxicillin/clavulanic acid can be used as a safe alternative.

Risk of venous thromboembolism

Pregnancy increases the risk of venous thromboembolism. The highest risk takes place during postpartum. Pregnant patients with IBD, especially those hospitalized with

active disease, have a 7-fold increased risk compared to pregnant patients without IBD. Therefore, low-molecular-weight heparin in prophylactic doses must be used in pregnant patients with IBD on relapse and/or hospitalized for whatever reasons (16).

SURGERY DURING PREGNANCY

Emergency surgery should be performed if clinically indicated regardless of the trimester. When possible, it should be performed at a center with neonatal and pediatric units and take a multidisciplinary approach (17). The main indication in UC is severe colitis unresponsive to medical treatment, and in CD, obstruction and perforation. A temporary ileostomy is preferred over primary anastomosis to reduce postoperative complications and need of reintervention (16).

MODE OF DELIVERY

Mode of delivery should be determined by the obstetric needs and planned during pregnancy considering the fear of perianal injury, nonhealing wounds, fistula, and damage to the pelvic floor. In vaginal delivery, episiotomy should be avoided because a high rate of perianal compromise has been reported. However, it is preferred over uncontrolled laceration. Here, advice from a gastroenterologist is of paramount importance.

Active perianal disease is the only exclusive indication for cesarean delivery because of the risk of suffering fecal incontinence due to the impact of vaginal delivery on sphincter and pelvic floor function. Having ileorectal and a pouch-anal anastomoses is just a relative indication (24).

POSTPARTUM AND BREASTFEEDING

The risk for disease flare-ups for postpartum mothers with IBD is about 20% and often occurs within the first 6 months. Medications should, therefore, be continued after delivery. It occurs more often in UC compared to CD.

Lactation does not independently affect disease activity. Besides, it might be protective against the development of early IBD in children. Mothers with IBD who are breastfeeding should follow standard nutritional recommendations such as increase

their caloric intake by 450-500 kcal/day and add 200 mg to 300 mg/day of omega 3 fatty acids from dietary sources. Mothers with ostomies or active disease may find it difficult to be well-nourished so they should receive nutritional counseling.

Sulfasalazine, thiopurines, and corticosteroids are of low risk to breastfed babies because of their low concentrations in human breast milk. A 4-hour delay after oral corticosteroids dosing is recommended to minimize exposure. Breastfeeding is also compatible with maternal anti-TNF agents based on minimal transfer rates in milk. Even if long-term prospective studies may be necessary, there is no association between biological maternal therapy during breastfeeding and infant infections. Based on limited experience, the concentration of ustekinumab and vedolizumab in breast milk seems to be minute so breastfeeding during therapy may be safe. However, it would be important to have more studies assessing the baby's immune system before making any solid recommendations. Although human studies are lacking, tofacitinib may also be avoided during breastfeeding because of the high concentrations reported in rat milk studies (22).

Treatment management during pregnancy and breastfeeding is summarized in the following table (Table 2).

CONSIDERATIONS IN NEWBORN BABIES

Family history is an important predictor of risk for acquiring IBD. Children of parents with IBD have an increased risk of developing the disease, especially in CD. Patients with a family history tend to develop it at an earlier age and show an increased concordance with the type of disease. Severity does not differ between family-related and sporadic disease.

Based on current knowledge, fetal exposure to most IBD drugs is considered safe for children except for methotrexate and tofacitinib. In babies exposed to anti-TNF therapy during pregnancy, current vaccination strategies with non-live vaccines do not differ from those of unexposed ones. However, since detectable levels of anti-TNF in the offspring are present within the first 6 months, live vaccines should be avoided in this period. If vaccinations are absolutely necessary because of imminent travel or exposure to a high-risk area it may be safe to measure anti-TNF serum levels (25).

These same recommendations regarding vaccines are adopted for vedolizumab and ustekinumab.

An important question here is how children exposed to IBD drugs fare in the long term. The PIANO registry followed children for up to 4 years, and they seemed to be doing well without an increased risk to their health or development (19).

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Table 1. Key aspects of managing IBD and pregnancy

Maintenance of disease remission is the main determinant of fertility and pregnancy success
Pharmacologic treatment that achieved disease control should be continued during pregnancy except for methotrexate and tofacitinib
Surgery in IBD and endoscopic procedures should be performed only when potential benefits take over the risks during pregnancy
The risk of venous thromboembolism in pregnant patients with IBD is higher compared to the general population
The mode of delivery should be determined according to the obstetric needs except for active perianal disease when cesarean delivery is mandatory
Most pharmacologic agents are safe during breastfeeding except for methotrexate and tofacitinib
If exposed to anti-TNF therapy during pregnancy, current vaccination strategies should not differ from those of unexposed patients except for newborn babies receiving anti-TNF in whom live vaccines should be delayed for, at least, 6 months

Table 2. Safety and considerations of IBD medications during pregnancy and breastfeeding

Medication	Pregnancy safety	Breastfeeding
5-aminosalicylates	Low risk	Low breast milk concentration
Corticosteroids	Low risk	Low breast milk concentration
Immunomodulators		
Thiopurines	Low risk	Low breast milk concentration
Cyclosporine	Low risk	Low breast milk concentration
Methotrexate	High risk. Stop 3 months prior to conception	Avoid
Biological agents		
Anti-TNF	Low risk (certolizumab does not cross the placenta)	Low breast milk concentration
Anti-integrin (vedolizumab)	Low risk	Low breast milk concentration
Anti-IL12-23 (ustekinumab)	Low risk	Low breast milk concentration
Oral janus kinase inhibitors (tofacitinib)	Not enough data. Ill-advised.	Not enough data. Avoid
Antibiotics	Low risk. Should be avoided beyond the first trimester (No problem with amoxicillin/clavulanic acid)	Low breast milk concentration

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