Reproductive Issues In Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is predominantly a disease of young people with a peak incidence between ages 20 and 40 years.[1] Indeed, for an adolescent or young adult this diagnosis can be devastating. Patients suddenly face a chronic incurable illness that may require lifelong treatment. Medication toxicity, the ability to lead a productive life, and life expectancy are common concerns for patients. In addition, given the age of affected individuals, reproductive issues are important concerns.

Patients may worry about their ability to conceive, the effect of their disease on pregnancy and the effect of pregnancy on their disease. They may also worry about the likelihood of passing IBD onto their children. "Am I going to be able to have a family? Will I find an understanding life partner? Will my children be healthy?" Patients with IBD frequently ask these questions of their physicians. It is therefore important that physicians understand the reproductive issues associated with IBD and manage them appropriately.

Fertility

Initial epidemiologic data suggested higher infertility rates and smaller family size in individuals with **Crohn's disease (CD)**.[2] These studies, however, did not take into account higher voluntary childlessness rates in patients with IBD. Voluntary childlessness, likely the result of fear of pregnancy and sexual avoidance, may be able to be reduced with sound medical advice along with psychological and psychosocial support.[3]

More recent studies have found infertility rates for men and women with IBD range from 5-14%, which is no higher than in the general population.[4] However, notable subgroups of patients do have compromised fertility. This includes patients who have undergone colectomy with ileal pouch construction[5] and potentially other IBD surgeries.[6] Infertility after surgery is likely due to adhesions in the pelvis and impaired tubal function. Laparoscopy, anti-adhesion gels, and "pexing" of the ovaries may prove helpful in preserving fertility, however, at this time it is very important that women who are considering surgery should be aware of this risk. Some may want to defer surgery until after childbearing.

Pregnancy does not significantly alter the course of pre-existing IBD or increase the risk of future complications.

Women with active inflammation may also have impaired fertility. Transmural inflammation in CD can create fistulas from the bowel to the vagina, uterus and ovaries. This may decrease fertility by causing painful intercourse or by impairing ovulation and implantation. CD may also invade the fallopian tubes and ovaries and impair ovulation or cause tubal occlusion. Weight loss and nutritional deficiencies may decrease fertility by causing dysmennorrhea or amenorrhea. Finally, feelings of disfigurement (e.g., from having an ostomy) or embarrassment (e.g. from excessive flatulence, fecal incontinence, perianal fistulas) may lower body image and sexual confidence in patients with IBD and thereby lower fertility.[7,8]

Male fertilty is affected by sulfasalazine use which reversibly decreases sperm count, impairs motility and alters morphology.[9] Low sperm counts are also caused by methotrexate.[10] Impaired fertility has also been described in some men who have undergone pouch surgery due to retrograde ejaculation and erectile dysfunction;[11] however, overall pouch creation has been found to improve male sexual function.[12]

IBD Inheritance

Many parents are concerned about the risk of passing IBD onto their children. This may influence their reproductive choices and behaviors. While the risk of IBD is higher in family members, heritability is still poorly understood.

The relative risk of IBD in first-degree relatives is 5 to 35 for CD and 10 to 20 for **ulcerative colitis (UC)**.[13] Ethnicity plays an important role in heritability with patients of Jewish origin having a higher age-adjusted IBD risk compared with non-Jews. This translates into a lifetime risk of approximately 5% for non-Jews and 8% for Jews for developing IBD if a parent has CD. Likewise for children of a parent with UC, the lifetime risk is approximately 2% for non-Jews and 5% for Jews.[13] Children with a parent with IBD are at highest risk of developing the same disease as their parent but they are also at increased risk for developing an alternate version of IBD.

There is no commercially available genetic test for IBD. Parents who are concerned about disease transmission should be aware that their children carry a higher risk of developing IBD than the general

Table 1. Food and Drug Administration Categories for the Use of Medications in Pregnancy

FDA Category	Definition
A	Controlled studies in animals and women have shown no risk in the first trimester and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester.
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease.
X	Studies in animal or humans show fetal abnormalities; drug contraindicated

population; however, due to environmental factors and other non-genetic factors accurately predicting a person's risk of developing IBD is difficult.

Pregnancy

Pregnancy does not significantly alter the course of pre-existing IBD or increase the risk of future complications.[14] It may even be protective.[15] Thus, pregnancy is not contraindicated in women with IBD.

Disease remission at the time of conception is very important. Women with inactive disease at conception have the same rate of relapse as non-pregnant women.[16,17] In contrast, women with active disease have a 70% chance of continued or worsening disease activity during pregnancy.[18]

While pregnancy doesn't affect the overall course of the disease, just having previous diagnosis of IBD, independent of disease activity, creates a high-risk pregnancy[19] with poorer pregnancy outcome than previously thought. Thus disease flares should be managed aggressively since IBD may lead to complications in both mother and baby. Maternal complications include bowel obstruction, hemorrhage, perforation, and sepsis. Risks to the baby include premature birth, low birth weight, small for gestational age and delivery by cesarean section (C-section).[20]

Treatment of flares in pregnancy follows the same guidelines as for non-pregnant patients with the added goal of inducing a rapid remission to maintain a healthy pregnancy. Budesonide, intravenous steroids, antibiotics, cyclosporine and anti-TNF agents have all been used to control disease activity in pregnancy. Women with medically refractory disease, toxic megacolon, or a high-grade stricture may require surgical intervention despite the risk inherent to surgery in pregnancy of miscarriages and premature birth.[21]

The mode of delivery in women with IBD is dictated by obstetric considerations. One exception is women with active perianal disease in whom C-section is advised. Vaginal delivery in these patients may further disrupt the perineum and injure the anal sphincter.[22] Notably, healed perianal disease and presence of an ileal pouch are not contraindications to vaginal delivery although some experts may advocate for C-section in the setting of an ileal pouch in order to preserve sphincter function.

Pregnant women with IBD should see their physicians regularly to allow for monitoring of disease activity, nutritional status and medication adherence. A successful pregnancy requires team effort with regular communication among the treating gastroenterologist, obstetric medicine specialist, obstetrician and/or maternal fetal medicine specialist. Rhode Island is unique in being able to offer this service. The "team approach" is being piloted at Women & Infant's Hospital for IBD and other serious illnesses in pregnancy in the High Risk Pregnancy Clinic.

Table 2. Safety of IBD Medications During Pregnancy and Lactation

DRUG	FDA Category	Recommendations for pregnancy	Recommendations for breast feeding
Adalimumab	B	Limited human data: low risk	No human data: Probably compatible
Amoxicillin/Clavulinic Acid	B	Low risk	Probably compatible
Azathioprine/ 6-mercaptopurine	D	Data in IBD, transplant literature suggest low risk	Limited human data: potential toxicity
Balsalazide	B	Low risk	No human data: potential diarrhea
Certolizumab pegol	B	No human data	No human data
Ciprofloxacin	C	Avoid: Potential toxicity to cartilage	Limited human data: probably compatible
Corticosteroids	C	Low risk: possible increased risk of cleft palate, adrenal insufficiency, premature rupture of membranes	Compatible
Cyclosporine	C	Low risk	Limited human data: potential toxicity
Fish Oil Supplements	--	Safe. Possibly beneficial	No human data
Infliximab	B	Low risk	Limited human data: probably compatible
Loperamide	B	Low risk	Limited human data: probably compatible
Mesalamine	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Contraindicated: Teratogenic	Contraindicated
Metronidazole	B	Given limited efficacy in IBD, risk of cleft palate, would avoid.	Limited human data: potential Toxicity
Natalizumab	C	No human data	No human data
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Rifaximin	C	Animal teratogen. No human data	No human data-probably compatible
Sulfasalazine	B	Considered safe. Give folate 2 mg daily	Limited human data: potential Diarrhea
Tacrolimus	C	Use if mothers health mandates	Limited human data: potential toxicity
Thalidomide	X	Contraindicated: Teratogenic	No human data: potential Toxicity

Adapted from Kane S. Caring for women with inflammatory bowel disease. *J Gender Specific Med* 2001;4:54-9.

IBD Medications in Pregnancy

Most patients with IBD require pharmacologic therapy to maintain disease remission. Since controlled disease at conception is key to maintaining remission through pregnancy, medication discontinuation before attempting to conceive is not advised. With few exceptions, medications should be continued during the pre-conception period and pregnancy. However, since definitive data on the safety of the drugs used to treat IBD are largely unavailable, it is important to carefully evaluate the risks and benefit of each medication with patients.

While the **US Food and Drug Administration (FDA)** categories provide some guidelines for medication use in pregnancy (Table 1) , the discussion regarding the drug use in pregnancy should extend beyond the FDA classifications to include post-marketing data and expert opinion. A comprehensive study evaluating long term effect of IBD and its medical therapy in pregnancy is underway nationwide, with two sites enrolling patients in Rhode Island.

The **5-aminosalicylates (5-ASAs)** are all FDA pregnancy category B except olsalazine, which is category C. They are generally considered safe for the treatment of mild IBD in pregnancy.

Corticosteroids (FDA category C) have been used extensively for the treatment of various inflammatory conditions in pregnancy. Early reports suggested an increased risk of oral clefts, especially when used during the first trimester.[23] However, subsequent studies as well as decades of clinical experience suggest minimal teratogenicity due to steroids.[24] Maternal hyperglycemia, macrosomia, and fetal adrenal suppression are potential complications of prolonged steroid use in pregnancy for which vigilant monitoring is required.[25]

The thiopurines (FDA category D), azathioprine and 6-mercaptopurine (6-MP) are used as maintenance therapy in patients with moderate IBD. Although animal studies have demonstrated teratogenicity, studies on their use in pregnancy in the transplant setting have not confirmed an increased risk of fetal malformations.[26] In addition, a study of pregnant women with IBD on thiopurines did not find any increase in preterm delivery, spontaneous abortion, congenital abnormalities or childhood cancer.[27] As a result most experts agree that the benefits of continuing these drugs in pregnancy outweigh their potential risks.[28]

Methotrexate and thalidomide are used for moderate or refractory IBD. Both are known teratogens and therefore FDA category X.[29] Furthermore, methotrexate is an abortifacient. These drugs should be used with extreme caution in young patients and discontinued for at least 3 to 6 months before conception.[28]

Cyclosporine (FDA Category C) is occasionally used in the treatment of fulminant UC. Studies in transplant recipients have not found it to be a significant teratogen. Its safety and efficacy has been described in a few case reports for steroid-refractory UC in pregnancy; but definitive safety data are lacking.

Prolonged antibiotics for the primary treatment of IBD are generally avoided during pregnancy. Patients with abdominal abscesses, phlegmons impending perforation, or fulminant colitis may however require them. The antibiotics used most commonly in IBD, ciprofloxacin (FDA category C) and metronidazole (FDA category B), should be used with caution. Animal studies have shown a potential risk for the quinolones to cause cartilage defects[29]and metronidazole has been shown to cause fetal malformations when given during the first trimester.[30]

Recently several monoclonal antibodies have been introduced for the treatment of IBD. Three anti-TNF agents and one anti-cellular adhesion molecules are approved by the FDA: infliximab (FDA category B), adalimumab (FDA category B), certolizumab pegol (FDA category B) and natalizumab (FDA category C). Infliximab and adalimumab have not been found to be teratogenic or associated with miscarriage;[31,32] but long-term safety data are lacking. Given that these drugs are relatively new and safety data are limited, patients may fear their use in pregnancy. While this is understandable, at this time women are not advised to abruptly stop treatment with an anti-TNF agent given the risk of precipitating a disease flare during pregnancy. Frank discussion of the benefits and potential risks of these drugs are needed.

Breastfeeding

Breastfeeding is unlikely to influence disease activity and may in fact be protective for the development of IBD.[33] However, many women with IBD choose not to breastfeed. Physician recommendations, the fear of medication transmission, and personal preferences are the most common reasons cited,[34] Physicians must therefore be aware of the actual risks so they can educate their patients.

Sulfasalazine, mesalamine and corticosteroids are considered compatible with breastfeeding[35]. There are no definite recommendations on lactation and azathioprine, 6-MP and anti-TNF use.

Conclusions

Reproductive issues are important for most young people with IBD. Preconception counseling is important and physicians should be prepared to initiate a frank discussion with their patients of reproductive age and answer questions about fertility and pregnancy. The association of IBD with maternal and fetal complications necessitates an aggressive approach in the management and treatment of these patients. The well known principle "healthy mother, healthy baby" certainly applies to the care of our pregnant IBD patients.

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Disclosure of Financial Interests

The authors have no financial interests to disclose.

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