Management issues in women with inflammatory bowel disease

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Medical practitioners caring for women with inflammatory bowel disease should recognize that gender may have a profound influence on patient perception of disease, body image, and clinical symptoms. These gender-related concerns as well as issues such as fertility and pregnancy increase the complexity of medical and surgical management of women with inflammatory bowel disease. This article reviews the important issues for practitioners to consider in taking care of women with ulcerative colitis and Crohn’s disease, focusing especially on body image, fertility, management of disease during pregnancy, and osteoporosis.

(Key words: Crohn’s disease, ulcerative colitis, inflammatory bowel disease, pregnancy, osteoporosis)

Inflammatory bowel disease (IBD) is a chronic inflammatory disease involving the digestive tract and is characterized by diarrhea, abdominal pain, and intestinal bleeding. It is associated with extraintestinal manifestations such as erythema nodosum, pyoderma gangrenosum, iritis, arthritis, ankylosing spondylitis, biliary tract disease, kidney stones, gallstones, and clotting abnormalities. The two principal types of idiopathic inflammatory bowel disease are ulcerative colitis and Crohn’s disease. In 5% of cases, the clinical features, endoscopic findings, and histology either alone or in combination may be inadequate to establish a clear diagnosis, leading to the designation of indeterminate colitis. The diagnosis of inflammatory bowel disease is made by clinical features with negative stool evaluations for bacteria and parasites, and radiographic or endoscopic examination with biopsies (or both) revealing characteristic features of ulcerative colitis or Crohn’s disease.

Patients with ulcerative colitis usually have bright red blood per rectum, often with mucus, cramps, and/or tenesmus and more frequent bowel movements. Inflammation of the colon occurs in a retrograde fashion from the rectum proximally, but it occasionally involves the terminal ileum in “backwash ileitis.” In approximately half of patients, the disease may affect only the rectum. In contrast, Crohn’s disease can involve any portion of the gastrointestinal (GI) tract. Crohn’s disease involves the colon alone 20% of the time; the small intestine alone, 30% of the time; and both small intestine and colon, 50% of the time. Inflammation can be patchy, resulting in skip areas. Clinically, IBD should be differentiated from chronic bacterial or parasitic infection, endometriosis, colonic malignancy, and colonic ischemia. The differential diagnosis of IBD is outlined in Figure 1. Treatment is determined by the type, location, and severity of disease. Various therapeutic regimens are outlined in Figure 2.

Although Crohn’s disease and ulcerative colitis occur equally in men and women, the gender of the patient affects certain issues that one should consider during patient care. For example, during various phases of the menstrual cycle, women with IBD may have an exacerbation of symptoms such as diarrhea and abdominal pain.1 A higher incidence of perineal disease has been noted in women than in men (A. E. Foxx-Orenstein, DO, personal correspondence). In women, fistulas to the vagina or uterus may develop. Moreover, gender also affects the patient’s perception of the disease, body image, pregnancy, and risk of osteoporosis.

Epidemiology

In the United States, approximately 1 million cases of ulcerative colitis and Crohn’s disease are present. The peak onset of disease occurs between age 20 and 40 years. Even after many years of research, the etiology of IBD has not yet been determined. However, it is clear that genetic predisposition plays a role in the development of Crohn’s disease and ulcerative colitis, though it is characterized by complex, nonmendelian inheritance.2,3 Yang and associates4 found that among patients with ulcerative colitis, 14% had a first-degree relative with ulcerative colitis, while 2% had a first-degree relative with Crohn’s disease. Among patients with Crohn’s disease, 12% had a first-degree relative with Crohn’s disease, while 7% had a first-degree relative with ulcerative colitis.
Body image in women with inflammatory bowel disease

Disease activity in IBD as well as medical and surgical treatment modalities can profoundly affect an individual's body image and sexuality. Medications can cause changes in appearance, and surgery may result in a stoma or scar perceived as disfiguring. In studies of the effects of IBD on lifestyle, 42% of patients reported that IBD adversely affected the general level of satisfaction in their lives, and 15% to 20% of patients reported dissatisfaction with their sexuality and body image.5,6 Body image and self-esteem may be affected by extra-intestinal manifestations of the disease, such as skin lesions or the presence of fistulizing disease. The loss of control of normal bodily functions as a result of fecal incontinence or the presence of the urgency to defecate may also adversely affect body image.

Surgery may result in disfiguring scars or an ostomy, whereas medical therapy with steroids may cause weight gain, fluid retention, acne, and increased facial hair.7,8 These side effects caused by medical and surgical interventions may determine a woman's preference or rejection of particular types of treatment. Sensitivity to these conflicts and concerns can help the medical practitioner deliver comprehensive care to the patient.

Sexual relations can be adversely affected in the presence of active IBD or by surgical treatment of IBD. Women with Crohn's disease and ulcerative colitis may have dyspareunia, and this condition and other factors may have an impact on the frequency or pleasure of sexual intercourse. In a study of 50 women with Crohn's disease, Moody and colleagues9 found that 24% of patients described infrequent or absent intercourse compared with 4% of age-matched controls. Dyspareunia, reported by 60% of patients with Crohn's disease, was a common reason for decreased frequency of sexual intercourse. Other reasons for decreased sexual activity included abdominal pain, diarrhea, and fear of fecal incontinence.9 Dyspareunia in patients with Crohn's disease may result from previous surgery, the presence of rectovaginal and enterovesicular fistulas, inflammation affecting the vagina, or abscesses in the perineal region.10 Similarly, in a study of

Figure 2. Medical management of inflammatory bowel disease based on severity of disease.
women with ulcerative colitis, 38% of patients reported having dyspareunia; however, this rate was not statistically significant when compared with that of a control group. Dyspareunia in these patients may be due to scarring from the disease itself or adhesions resulting from surgery.

Continence-sparing surgical techniques such as ileal pouch–anal anastomosis have resulted in improvement in sexual function and quality of life and is presently the surgical procedure of choice in most patients requiring proctocolectomy. In a study of 92 women undergoing restorative proctocolectomy, 85% of respondents reported moderate to extremely satisfying sexual relationships. Long-term results for this procedure reveal a favorable outcome in a majority of patients. Several studies also indicate that in women who undergo ileal pouch–anal anastomosis, pregnancy and childbirth are well tolerated, do not compromise pouch function subsequently, and are not affected by the type of delivery (vaginal versus cesarean section).

Physicians can help a patient cope with these issues by openly discussing them in the course of routine appointments as well as by providing and recommending informational materials. Education and support groups can help patients cope with chronic disease and adjust to the consequences of medical and surgical treatments of IBD. Although nurses and physicians may discuss hygiene and alternative methods of sexual intimacy, patients ultimately may find that support groups sponsored by organizations such as the Crohn’s & Colitis Foundation of America can help them cope with the dramatic changes induced by surgical therapy for IBD. Figure 3 provides a list of resources for patients with IBD.

Effect of inflammatory bowel disease on fertility

The peak onset of IBD occurs during the reproductive years. Health providers should therefore be aware of the consequences of IBD on fertility and pregnancy. Despite the potential complications of pregnancy in the setting of active IBD, the majority of individuals with IBD maintain normal reproductive function and will deliver normal full-term infants. It is a common misconception that women with IBD are less fertile than the general population. Fear of pregnancy may also be an important factor in voluntary childlessness and may result from concern about potential teratogenic effects of medications or pregnancy complications as a result of the disease. Perianal disease may result in dyspareunia and hence decreased frequency of intercourse. Many studies, however, have shown that when adjusted for age, frequency of intercourse, and voluntary childlessness, fertility rates are comparable to those of the general population. Researchers concur that women with ulcerative colitis have normal fertility, but some studies suggest that fertility in Crohn’s disease may be decreased in proportion to disease activity and degree of inflammation. Colonic and rectal inflammation in Crohn’s disease may extend to the ovaries and fallopian tubes and impair their proper function. Infertility may be more common after surgery for IBD. In general, the risk of infertility is increased in patients undergoing ileal pouch–anal anastomosis compared with patients undergoing abdominoanal colectomy or resections of the small bowel. Why patients undergoing anal ileal pouch–anastomosis are less fertile is not known. It is possible that adhesions and fallopian tube scarring may impair fallopian tube function.

Effect of inflammatory bowel disease on pregnancy

Physicians should advise patients with IBD to defer conception until disease is in remission. Then, patients are likely to have an uncomplicated pregnancy with no increase in the risk of spontaneous abortion, low birth weight, stillbirth, and congenital anomalies in comparison to healthy women. Several population-based studies in Sweden and Denmark revealed an increased incidence of preterm birth and lower birth weight in babies born to mothers with IBD, particularly in women with Crohn’s disease. These studies, however, were retrospective, had limited information on the degree of disease activity during pregnancy, and yielded results that were not clinically significant. In another retrospective study, Fedorkow and coworkers found that women with a history of IBD had an increased risk of preterm birth, and this risk was increased even further if active disease was present during pregnancy. Therefore, every effort should be made to achieve and maintain disease remission before conception. The ideal duration of remission before conception is unclear.

Effect of pregnancy on inflammatory bowel disease

Disease activity during pregnancy is affected by the disease activity at the time of conception. Pregnancy itself does not appear to increase the rate of relapse of otherwise quiescent ulcerative colitis or Crohn’s disease. In fact, rates of relapse in pregnant women with ulcerative colitis and Crohn’s disease are similar to those in nonpregnant women. In a retrospective review, Miller examined the effects of pregnancy on IBD disease activity in eight studies involving 528 pregnancies in patients with ulcerative colitis and four studies of 186 pregnancies in patients with Crohn’s disease. In patients with inactive disease, 73% of women with Crohn’s disease and 66% of patients with ulcerative colitis had no episodes of relapse during pregnancy. The presence of active disease, however, resulted in worsened or continued activity in 65% of patients with Crohn’s disease and 69% of patients with...
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Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in the first trimester (and there is no evidence of a risk in later trimesters).

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of use of the drug in pregnant women clearly outweighs any benefit. The drug is contraindicated in women who may become pregnant.

ulcerative colitis. Most studies suggest that if relapse occurs, it is more common during the first trimester for ulcerative colitis and in the first and second trimester and puerperium for Crohn’s disease.

The type of delivery (vaginal vs cesarean section) in women with Crohn’s disease is commonly an issue for obstetricians. It is generally agreed that patients with perirectal abscess or rectovaginal fistulas should undergo cesarean section. Whether all patients with perianal fistulas should undergo a cesarean section is not clear. One study by Brandt and associates showed that in 18% of patients, perineal involvement developed after vaginal delivery if episiotomy was performed. Other studies have not duplicated these results. If there is no history of perianal disease or if perianal disease is inactive at the time of delivery, women may undergo normal vaginal delivery because the risk of perianal disease relapse or disease of new onset is low.

Management of inflammatory bowel disease during pregnancy
Management of IBD during pregnancy should be guided by the principle that active disease poses the greatest threat to pregnancy and outweighs the risks of treatment. At present, there exist limited data on the safety of most medications used to treat IBD in pregnancy because studies in pregnant women have not been done. Medications are presently classified as to their safety based on data from animal studies and clinical trials. The current drug safety classifications are listed in Figure 4.

Studies reveal that many medications used for symptomatic relief of diarrhea in patients with IBD such as loperamide hydrochloride and diphenoxylate hydrochloride are safe to use during pregnancy. The use of loperamide during the first trimester does not result in fetal malformations or spontaneous abortions. Although a few case reports suggest that diphenoxylate may cause congenital anomalies, data from larger studies do not support an association between the drug and congenital anomalies.

Oral anti-inflammatory medications such as sulfasalazine and mesalamine are safe to use in the treatment of IBD during pregnancy. Sulfasalazine crosses the placent but has not been associated with fetal abnormalities. However, patients taking sulfasalazine should receive additional folate supplementation to decrease the risk of neural tube defects. In male patients with IBD, treatment with sulfasalazine results in decreased fertility due to decreased sperm counts and motility and morphologic abnormalities. Quality of sperm returns to normal within 3 months after cessation of therapy. Several prospective studies have shown that mesalamine and other 5-aminosalicylic acid (5-ASA) agents may be used safely in pregnancy. Habal and associates reported that there were no fetal abnormalities in 17 women with IBD who were treated with 5-ASA agents during pregnancy. In a larger study, Diav-Citrin and associates reported that in 165 women exposed to mesalamine during pregnancy, there was no significant increase in the incidence of congenital malformations compared with that in a control group matched on the basis of cigarette smoking and alcohol consumption.

Corticosteroids have not been shown to be associated with congenital defects in human studies. In a large series of pregnant women with IBD who were treated with steroids, the rate of fetal complications was lower than in the general population. Therefore, steroids may be used in pregnant women with moderate to severe disease during pregnancy.

Although no large studies have been done to examine the use of immunomodulatory agents such as 6-mercaptopurine,

**Figure 4. Classification of drug safety in pregnancy as used by the Food and Drug Administration. (Source: Federal Register 1980;44:37434-37467.)**

| CATEGORY A | Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of harm to the fetus appears remote. |
| CATEGORY B | Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in the first trimester (and there is no evidence of a risk in later trimesters). |
| CATEGORY C | Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. |
| CATEGORY D | There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). |
| CATEGORY X | Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of use of the drug in pregnant women clearly outweighs any benefit. The drug is contraindicated in women who may become pregnant. |
azathioprine, and cyclosporine for treatment of IBD during pregnancy, a few case series do suggest that their use may be safe in pregnancy. The use of these agents is justified if the pregnant woman has active disease refractory to other oral or topical agents.\(^{10,32}\) Methotrexate is contraindicated in pregnancy because of its teratogenic effects. At present, few data are available with regard to the teratogenic effects of infliximab (Remicade), an immunomodulatory agent currently used in refractory or fistulizing Crohn’s disease; however, a few case reports suggest that use of infliximab may be safe in pregnancy.\(^{13}\) Figure 5 lists medications and notes their safety during pregnancy.\(^{28}\)

Monitoring of disease during pregnancy can be problematic in patients with active disease. Laboratory studies including complete blood cell count and markers of inflammatory activity such as C-reactive protein level and erythrocyte sedimentation rate (ESR) can be helpful in confirming whether a woman is having a flare of IBD. However, ESR and C-reactive protein levels may be elevated during pregnancy while the hematocrit may be decreased. Radiologic studies are usually avoided in pregnant women because of concern about radiation exposure; however, if clinically warranted, kidney ultrasound biopsy and computed tomography scans should be performed. Use of ultrasound examination and magnetic resonance imaging are safe in pregnancy.

Ultimately, endoscopy may be necessary to assess disease activity. In a retrospective study of the experience of sigmoidoscopy and colonoscopy in 54 patients, Cappell\(^{34}\) concluded that sigmoidoscopy does not induce premature labor or result in congenital anomalies, low birth weight, or fetal demise. Sigmoidoscopy was particularly beneficial in pregnant patients in evaluation of lower gastrointestinal bleeding. Thus, sigmoidoscopy during pregnancy appears to be safe and may be done in stable patients with important clinical indications such as the evaluation of rectal bleeding, the assessment of symptoms refractory to medical therapy, or to rule out infection. Several studies suggest that colonoscopy may be done safely in pregnant women. Colonoscopy is more difficult to do in pregnant women because of displacement of the colon by the uterus, and safety considerations may complicate the choice of sedation. If purely elective, colonoscopy should be delayed until the postpartum period, but it may be needed for diagnosis if findings of flexible sigmoidoscopy are not diagnostic.

### Osteopenia and osteoporosis

An important consideration in women with IBD is the treatment and prevention of osteopenia and osteoporosis, which are not only common in postmenopausal women, but which are also potential complications of IBD, malabsorption, and medical therapy for IBD. Osteopenia is a reduction in bone mass between 1 SD and 2.5 SD below peak bone mass, whereas osteoporosis is a reduction in bone mass greater than 2.5 SD below peak bone mass. Osteoporosis increases the risk of fracture, particularly in trabecular bone found in the vertebrae, ribs, pelvis, and the ends of long bones. Osteopenia is present in approximately 29% to 78% of patients with IBD, and osteoporosis is present in 23% to 60% of patients with IBD.\(^{35-37}\) Although some studies suggest that patients with Crohn’s disease may be at greater risk for these conditions, several studies indicate that the degree of reduced bone mineral density is similar in patients with ulcerative colitis and Crohn’s disease.\(^{38}\)

Potential risk factors for osteoporosis in women with IBD include low body mass, decreased calcium intake resulting from avoidance of dairy products, reduced physical activity, smoking, elevated levels of cytokines such as interleukin 6, interleukin 1, and tumor necrosis factor, all of which may contribute to the development of osteoporosis. Particularly in patients with Crohn’s disease, malabsorption can lead to vitamin D deficiency and loss of calcium in stool. Furthermore, the use of steroids and cyclosporine can exacerbate bone loss through their effects on calcium metabolism and bone resorption. Most studies show that osteoporosis in patients with IBD correlates with steroid use.\(^{38-41}\) The influence of steroids on bone loss is dependent on duration of therapy as well as on the dose of steroids. With high-dose steroids, bone loss may be rapid, occurring at a rate of 5% to 15% per year. The greatest decrease in bone density is observed in the first 6 to 12 months of therapy. Some studies suggest that reduction in bone mineral density (BMD) may be more pronounced in men treated with glucocorticoids than in premenopausal women. The reasons for this gender difference are unclear, but some investigators have suggested that men may be more sensitive to the effects of glucocorticoid therapy compared with women.\(^{36,41}\)

Primary care physicians caring for women should be aware of the increased risk of osteoporosis among patients with IBD and other gastrointestinal disorders. Because of this risk, special attention should be paid to diagnosis, treatment, and prevention of osteoporosis. A diagnostic approach should include measurements of bone density by dual-photon absorptiometry done at the hip and spine at baseline and after 1 year of corticosteroid treatment or after 1 to 2 years of active IBD. Additional assessment should include measurement of serum calcium, parathyroid hormone, and 25-hydroxyvitamin D levels. Emphasis should definitely be placed on prevention of osteoporosis, which can be achieved by weight-bearing exercise, increased intake of dietary calcium (1000 mg/d to 1300 mg/d depending on age) and vitamin D (400 IU/d to 800 IU/d), and smoking cessation. In all patients who require steroid therapy, an attempt should be made to use steroids at the lowest effective doses for the minimal amount of time. Steroid-sparing medications such as azathioprine or 6-mercaptopurine should also be used in an attempt to reduce the dose and duration of corticosteroid therapy.

For patients with established osteopo-
nia or osteoporosis, consideration should be given to treatment with drugs to prevent further bone loss and to potentially increase bone mass. Calcium supplementation should be provided to all women with chronic gastrointestinal disease that could impair calcium absorption. Of the calcium supplements, calcium citrate has the greatest bioavailability and can be administered at a dose of 600 mg twice a day. Patients with malabsorptive syndromes or patients who have undergone extensive ileal or jejunal resection likely will need extra vitamin D supplementation. Vitamin D can be given intramuscularly or as an oral supplement. In postmenopausal women and even in patients with established osteoporosis, estrogen replacement therapy can result in increased bone mass. Other agents such as calcitonin and bisphosphonates (such as alendronate sodium [Fosamax] and risedronate sodium [Actonel]) act by inhibiting bone resorption.\textsuperscript{37} Parathyroid hormone is another potential treatment modality that will soon be available. The choice of these various modes of therapy is determined by the patient’s risk factors for osteoporosis, the use of modes of therapy such as steroids and cyclosporine that may further accelerate bone loss, and the potential for pregnancy-related complications.

Bisphosphonates may also be used for the prevention of glucocorticoid-induced osteoporosis. Two large randomized, placebo-controlled trials in men and women receiving glucocorticoid therapy revealed that alendronate sodium at doses of 5 mg/d and 10 mg/d slightly increased bone density.\textsuperscript{37} Studies using risedronate have shown similar protective effects. In patients with either established osteopenia/osteoporosis or multiple risk factors for osteoporosis who require treatment with glucocorticoids, strong consideration should be given to the use of bisphosphonates for the prevention of osteoporosis. Many physicians avoid using bisphosphonates in patients who are planning pregnancy because of their unknown long-term effects on the fetus.

Comments
This article highlights a few of the considerations and challenges in the care of women with IBD. Management of women with IBD requires special knowledge of the effect of IBD on pregnancy, the effect of pregnancy on IBD, and the safety of medications in pregnancy. Recognition of the health needs and psychological concerns of women with Crohn’s disease and ulcerative colitis will help medical practitioners deliver safe and effective care to women with these disorders.

References