

Notes from “Inflammatory Bowel Disease with Special Considerations for Women” Slide Lecture

Inflammatory Bowel Disease: Overview [Slides 1-8]

Slide 1

Inflammatory bowel disease, or IBD, profoundly affects the day-to-day health, quality of life, and prospects for survival of more than 1 million persons in the United States and millions more worldwide.

This presentation pays particular attention to IBD in women, in whom this disease requires special consideration.

Slide 2

IBD comprises 2 distinct disease entities: Crohn’s disease, or CD, and ulcerative colitis, or UC. Both of these diseases are heterogeneous inflammatory disorders whose etiology is not fully understood but that result from chronic up-regulation of the enteric mucosal immune system.¹ The lesions of CD may appear throughout the gastrointestinal tract, from the mouth to the anus, whereas UC is confined to the large intestine.^{2,3}

Overall, the prevalence of IBD appears to have a bimodal distribution. There are estimated to be more than 1 million cases in the United States, approximately evenly divided between UC and CD.⁴

Onset is most common in the second and third decades of life, with a second, smaller peak in the sixth decade.⁵

The incidence of IBD is approximately equal in males and females, with a slightly higher risk for women than for men; males have a 20% higher incidence of UC than females, and females have a 20% higher incidence of CD than males.⁵

Slide 3

The impact of IBD on healthcare is significant. IBD is the reason for 700,000 physician visits and 100,000 hospitalizations each year, two thirds of these being for CD.

Both CD and UC are chronic, lifelong diseases characterized by alternating flare-ups and remissions whose management may eventually become more complicated. Over their lifetimes, approximately 50% to 80% of patients with CD will require surgical treatment. Since no definitive cure is currently available for either disease, treatment focuses on symptomatic control and maintaining quality of life.^{5,6}

Slide 4

The empiric risk for developing CD based on genetic factors is shown. A child whose parents both have CD has a 50% risk of developing the disease. If one of identical twins has CD, the chance that the other twin will develop the disease is 37%. Among Ashkenazic Jews, if a sibling has the disease, the chance that the other sibling will develop CD is 16.8%. The risk for several other genetic relationships declines below 10%. The risk in the general population is 0.1%.⁷

Slide 5

A study of 343 men and women using an instrument designed to identify the differences between the concerns of female and male patients with IBD reported that women noted significantly higher levels of symptom severity. Women's levels of concern with IBD were much higher than those of men.⁸

Slide 6

This table lists concerns relating to IBD that were felt more strongly by women than by men and those in which sex differences did not matter.

Those felt more intensely by women included feelings about their bodies, a loss in sense of attractiveness, feeling alone, and concern about having children and, for women with CD but not UC, about intimacy and sexual performance. With regard to sexual performance, men with UC reported slightly greater levels of concern than did women. However, women with CD had much higher levels of concern about sexual performance than did men.⁸

A study using the Rating Form of IBD Patient Concerns reported that women had higher levels of concern in all 4 indices used – impact of disease, sexual intimacy, complication, and body stigma. It was suggested that the differences for sexual intimacy and disease complications were largely explained by differences in disease severity.⁹

All patients, regardless of sex, are concerned with loss of energy, the effects of medications, the possibility of surgery, and the issue of being a burden to caregivers.

Aside from the gender differences, there are important differences in the concerns of CD and UC patients. Because of the increased likelihood that they will develop cancer (the cumulative incidence of colorectal cancer in patients with pancolitis over 35 years is as high as 25%), that particular eventuality ranked high among the concerns of UC patients. In patients with CD, the chief concern was the uncertain nature of their disease, likely owing to the frequency of recurrences and flare-ups.^{3,9,10}

Slide 7

Fertility in women may be affected by surgery, including ileal pouch-anal anastomosis, or IPAA. If women are in the active disease state at the time of conception, there is an increased risk of relapse. For men, the only comparable concern is with sperm viability when taking sulfasalazine.¹¹ Questions have been raised about the impact of 6-mercaptopurine – 6-MP – on male fertility, although the sperm quality is normal.^{12,13}

As stated earlier, women have a higher level of disease-related concerns, primarily because of greater disease severity. Finally, sexual activity is more affected in women than in men. Women are more subject to pain during intercourse, and men may experience a postsurgical decline in libido.

Slide 8

Patients with IBD frequently suffer from other chronic inflammatory diseases that affect other organ systems. The course of these diseases often runs independently of the course of IBD; however, they occur so frequently in patients with IBD that, rather than being

regarded as comorbidities, they are seen as extraintestinal manifestations of the underlying disease.

Eye inflammations – iritis and uveitis – were the most common extraintestinal diseases found in a Canadian population-based survey, affecting about twice as many women as men. Primary sclerosing cholangitis was more common among men than among women with UC, as was ankylosing spondylitis. Among skin lesions, pyoderma gangrenosum was equally prevalent in men and women, but erythema nodosum was more common in women than in men. Overall, 6.2% of patients had 1 of those 6 major extraintestinal diseases.¹⁴ In some referral centers, however, the reported incidence has been as high as 21% in patients with UC, 42% in those with either UC or Crohn’s colitis, and 23% in those with CD confined to the small bowel.^{15,16}

Additional systemic complications include reduced bone mineral density, or BMD, related to increased bone resorption without an increase in bone formation. This is more prevalent in women than in men and is independent of corticosteroid intake.¹⁷

Other extraintestinal manifestations include gallstones, kidney stones, liver inflammation, and arthritis.¹⁵

Fourteen percent to 88% of children with IBD are reported to have subnormal growth even before the time of initial diagnosis. Growth retardation may continue because of both malabsorption and reduced nutritional intake and because of growth-suppressing drugs such as corticosteroids.¹⁸

Special Considerations for Women with IBD [Slides 9-10]

Slide 9

Women have a higher degree of concern than do men about the effects of IBD on their health and quality of life. Many of these concerns relate specifically to reproductive issues.

Slide 10

Clinicians need to be aware of special considerations that affect women with IBD. Women are particularly concerned with the relationship of IBD to menstruation, contraception, body image and sexuality, conception and pregnancy, and menopause with its accompanying issues.

Finally, the existence of concurrent irritable bowel syndrome, IBS, is somewhat common in women, sometimes even confounding the diagnosis of IBD. In general, IBS occurs more often in women, and its symptoms overlap with those of IBD.

IBD: Issues with Menstruation and Contraception [Slides 11-19]

Slide 11

There are questions regarding the impact of IBD on menstruation and contraception (and vice versa).

Among these are:

- Does IBD affect the menstrual cycle, and does the menstrual cycle impact disease symptoms?
- Similarly, is there a relationship between oral contraceptives and IBD disease symptoms?

Slide 12

The bowel habits of healthy women change during various phases of the menstrual cycle. However, women with IBD have a higher prevalence of bowel-pattern fluctuations.

It has been suggested that the physiologic mechanism for the higher incidence of bowel-pattern fluctuations may be increased intestinal prostaglandin production, which results in contraction of colonic smooth muscle. Additionally, diarrhea may be caused by increased intestinal secretion and altered electrolyte absorption or by changing levels of progesterone.¹⁹

Although gastrointestinal symptoms are commonly part of the premenstrual syndrome, women with IBD and IBS complain of these symptoms much more than does the general population. Some women consider these “miniflares” of their underlying disease; however, rather than treating these symptoms as indications that disease is worsening, symptom control may be more appropriate, since symptoms will often resolve in a few days. For women whose symptoms are particularly debilitating, suppression of menses is the only way to provide relief. This may be achieved with injectable contraceptives or gonadotropin-releasing hormone analogs.²⁰

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The symptoms experienced during the menstrual cycle that may be increased in women with IBD include nausea, vomiting, back pain, urinary frequency, and mood changes such as depression or anxiety.

In a retrospective study of 49 women with UC, 49 with CD, 46 with irritable bowel syndrome, and 90 controls, the symptoms reported most frequently are pelvic pain, lower back pain, diarrhea, irritability, and headache.²¹ The incidence of any menstrual symptom in this study was significantly higher for women with IBD than for controls.

Slide 14

Women with CD tend to be more affected by increased symptoms during menstruation than are women with UC, and women with CD experience diarrhea significantly more than do women without IBD.²¹

Slide 15

Although the data may not provide a definitive answer, 3 questions about the relationship between oral contraceptives, or OCs, and IBD must be addressed:

- First, is there evidence of an increased incidence of CD with use of OCs?
- Second, are OCs related to flare activity in CD?
- Finally, is the introduction of newer OCs with a lower estrogen content associated with a decreasing incidence of CD in women?

Slide 16

This graph tracks the percentage of 331 women with CD who experienced flares over a period of 500 days. The upper line represents patients who are taking OCs, and the lower line represents those not taking OCs. There is a small difference approximately midway

through the study; however, by the end of the study period, this difference has largely disappeared. During the study, 61 of 134 OC users (46%) had flares, compared with 85 of 197 non-OC users (43%). The study also confirmed the harmful effect of smoking but showed that the use of OCs had no effect on CD activity.²²

Slide 17

This graph tracks the female-to-male ratio for CD incidence for 2 population cohorts, and also for OC use, beginning in 1960. Starting in 1964, there was an increase in CD incidence in both cohorts. OC use declined somewhat in the mid-1970s because of increased concern among American women about side effects. Also by the mid-1970s, most women were using OCs with a lower estrogen dose – 50 µg rather than 100 or 150 µg as was formerly common. CD rates declined thereafter, despite a continued increase in OC use. If OCs have contributed to the increased prevalence of IBD, a possible explanation for the post-1975 decline in CD may be the change in OC formulation to a lower estrogen content. It has also been suggested that previous rather than current OC use is more strongly associated with relapse in CD.²³

Slide 18

In addition to their potential interactions with IBD, OCs are contraindicated for all women with histories of thromboembolic disease, those with any hepatic disease resulting in elevated liver enzymes, those with histories of breast cancer, smokers more than 35 years of age, and women who are pregnant.

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In summary, women with IBD who want to take OCs should use OCs with lower estrogen levels. In addition to all of the standard contraindications for OCs, women with IBD and comorbid liver disease or hypercoagulability should especially avoid OC use.

IBD: Issues with Body Image and Sexuality [Slides 20-29]

Slide 20

Women with IBD tend to be more concerned with issues of body image and attractiveness than do men with IBD. A survey of 343 men and women with IBD, using the Rating Form of IBD Concerns, reported that women rated feelings about their bodies 8th (from a list of 25) among their concerns, whereas men rated that concern 12th. Women rated attractiveness 13th, and men rated that concern 20th. Conversely, men rated both sexual drive and sexual performance higher than did women.⁸

Slide 21

Both disease manifestations and the impact of treatment can have an enormous effect on a woman's sexuality. Between 20% and 80% of patients with CD are likely to experience perianal complications, including fistulae. Patients' principal concerns with these lesions are with difficulties in keeping the anal area clean and with disfigurement. In addition, surgical removal may lead to persistent ulceration and drainage.²⁴

Among skin lesions affecting patients with IBD, pyoderma gangrenosum is particularly painful and disfiguring. About one third of patients with pyoderma gangrenosum have comorbid IBD, evenly divided between CD and UC.²⁵ IBD can cause pain and fatigue, both of which can affect a woman's sexual drive and performance.

IPAA with reconstructive proctocolectomy is currently considered the preferred surgical option for the management of IBD. It removes the need for permanent stoma and

provides a natural means of defecation without the need for an ileostomy bag. Some studies have reported an improvement in quality of life after IPAA.²⁶

Approximately 20% of patients with IBD develop some form of peripheral arthritis, which can lead to deformities and limited mobility.²⁷

Slide 22

In any discussion of human sexuality it is important to recognize that the survival of the species is not why humans engage in sexual activity. The psychological aspect of sexuality, which involves sexual drive, emotions, communication, and the pleasurable sensations connected with sexual activity, is of greatest importance to humans.

Both sex and defecation are personal and private, and lack of open discussion may facilitate the social stigma attached to IBD. Fears regarding conception, attractiveness, and the impact on personal relationships often prevent patients from communicating openly. However, communication is key in overcoming the psychological impact of IBD. Patients should be encouraged and counseled to discuss their feelings with their spouses and vice versa.

There is evidence that CD is associated with significant sexual dysfunction, resulting in decreased frequency of sexual intercourse. Many more women with CD are entirely inactive sexually primarily because of pain, diarrhea, and fear of fecal incontinence during intercourse.²⁸

A woman may feel dirty because of her incontinence and, consequently, not feel sexy or attractive. Self-esteem is often reduced, and a woman can feel that she has lost her former identity. In the case of women encountering potential new sexual partners, there is also anxiety regarding disclosure of the condition.

Slide 23

The categories into which most women's sexual concerns after IBD surgery fall are body image, sexuality, communication, fertility, and pregnancy. Alteration of the patient's body in any manner may affect her self-perception, which may lead to difficulties in sexual health and interpersonal relationships. Although surgery can affect sexual function, the prognosis for improvement is much better when partners are involved throughout the surgical process.

Slide 24

The current preferred surgical modality for UC is IPAA. In 1 study, overall quality of life following this procedure was significantly increased beginning 2 years after surgery.²⁶ Quality of life has been assessed as being excellent for 90% of patients.²⁹ An improvement in quality of life contributes to improved sexual function. A study of 762 men and 692 women who underwent IPAA reported that 25% of patients had improved levels of sexual activity.²⁹

Another study of sexual function after IPAA produced similar results. Sexual function improved by 16% and frequency of intercourse by 35%.³⁰

Some problems, such as dyspareunia, vaginal drying, and fecal leakage during intercourse, can occur after surgery.

Slide 25

The majority of women who have undergone restorative proctocolectomies with IPAA are satisfied with their sexual relationships. A questionnaire was sent to all women who had undergone this procedure by 1 surgeon during a 10-year period, yielding 92 responses. The percentage of women reporting that their sexual relationships with their partners were improved was 22.5%, and 51.3% considered their relationships unchanged. Although 26% felt that their relationships were less satisfactory, 86% felt their relationships were moderately to extremely satisfactory. It was suggested that for many women, the degree of satisfaction may have declined from “extremely satisfied” to “moderately satisfied.”³¹

Slide 26

This table shows changes in gynecologic functions after IPAA, based on a questionnaire sent to all 203 women (of whom 110 responded) who had IPAA at a clinic in Massachusetts between June 1980 and December 1991. Dyspareunia tripled, fecal incontinence increased from 3% to 7%, and menstrual problems increased from 23% to 31%.³² A smaller, Swedish study found a lower percentage of dyspareunia, with 4 (7.5%) of 30 women reporting this problem.³³ In an additional study, dyspareunia doubled after IPAA, from 11.4% before surgery to 22% after ($P<.002$).³⁴ Thus, although IPAA is associated with an improvement in postoperative quality of life,²⁹ it is not without negative impact.

Slide 27

Ileostomy, in contrast with IPAA, requires the creation of a permanent stoma in the abdominal wall and the use of an external fecal pouch. The impact of this procedure on sexual function is greater than that of IPAA. Nevertheless, in a questionnaire-based study of 82 women who had had ileostomies, the largest percentage of patients, 47%, reported that their sexual function was unchanged. Another 47% reported that their sexual function was affected adversely – 14% severely, 11% moderately, and 22% mildly. For the small percentage who reported an improvement in sexual function, the reason may be improvement in their disease symptoms and overall well-being.³⁵

Slide 28

The greatest cause of concern for patients with ileostomies is the appliance itself. A study of 50 patients with ileostomies who were considered to be well rehabilitated reported that nearly three quarters of patients viewed the appliance as a physical hindrance to sexual activity and a potential source of embarrassing leakage. More women than men stated that they felt less sexually desirable or attractive since surgery. By a ratio of about 2 to 1, respondents reported that the presence of the stoma did not make sexual intercourse more difficult. Equal percentages reported that the presence of the stoma made sexual intercourse psychologically more difficult.³⁶

Slide 29

The feelings and concerns about their bodies of women with IBD are strongly affected both by their disease and by medical interventions, particularly surgery.

Both gastrointestinal and extraintestinal symptoms have important impacts on body image. These include perianal complications, disfiguring and painful skin lesions, and arthritic complications.

Patients who have ileostomies are adversely affected in terms of body image, even though their overall quality of life may improve. In particular, the presence of stoma and the need to use an external device for collection of feces contribute to a negative body image.

Improvement in quality of life following successful treatment spills over into improvement in sexual activity, in terms of both frequency and quality. However, even after successful surgical management, problems persist, such as pain during intercourse and some fecal leakage.

Clinicians therefore need to be aware that even after treatment that is judged to be successful by current medical standards, there may still be a continuing call for caring attention to the body image and sexual needs of their female patients.

Conception and Fertility in Women with IBD [Slides 30-36]

Slide 30

How do IBD and its treatment affect a woman's ability to conceive a child?

Slide 31

Overall, IBD appears to have a minor impact on fertility. A 20-year study evaluating data from 147 women with UC reported that 92.2% of women who wanted to conceive were fertile³⁷ and that the involuntary infertility rate of 6.8% was no higher than that in the general population.³⁷ Many women with UC refrain from attempting to become pregnant out of fear that the pregnancy may be difficult or have a poor outcome.³⁸

A questionnaire-based study analyzing data from 197 women with CD and 107 women with UC concluded that there was no significant reduction in fertility associated with IBD.³⁸ In this study, it was learned that more patients with IBD than controls chose not to have children. Women with IBD reported that they were afraid to have children or had been advised not to have children. Women with CD were advised that they might have more difficulty having children than would women with UC.³⁸

The inflammation of CD near the terminal ileum can occasionally affect the ovaries and fallopian tubes³⁹ and even induce occlusion of the uterine tubes.⁴⁰

In men, long-term treatment with sulfasalazine has been shown to result in decreased semen quality. This effect can be reversed when treatment is discontinued.^{11,41} In male rats, methotrexate has caused temporarily lowered sperm counts.⁴²

Concerns have been raised about the teratogenic potential of azathioprine, or AZA, and its active metabolite, 6-MP. The quality of male sperm in patients taking these immunomodulators is normal.^{12,13} One 4-year-old child whose father had been taking 6-MP at the time of conception was diagnosed with a tumor of the kidney. The tumor was removed with no metastasis, and the child was doing well at 4-year follow-up.⁴³

Slide 32

As with UC, the reported rates of fertility in women with CD conflict. The limitations described earlier apply to these studies, relating to the short period of observation or follow-up and to voluntary childlessness due to uncertainty regarding outcomes.³⁸

A study with 77 married patients of childbearing age found that 25, approximately 33%, were infertile, despite having tried to achieve pregnancy for 2 years or longer. Chances of infertility were greater ($P < .01$) in patients with Crohn's colitis than in those with small-bowel involvement.⁴⁴

Fertility rates in 53.5% of 86 women with CD were reduced in another study, and this was linked to the disease site; 66.7% of those with large-bowel involvement could not conceive compared with 50% of those with small-bowel involvement only.⁴⁵

A study evaluating 78 patients with CD also found that 67% could not conceive. This was based on the fertility rate in the study group compared with that in the US population. In this group, although the fertility rate for women with colon involvement was not greatly different from that in the US population, the fertility rate for women with small-bowel involvement was markedly lower – .053 pregnancies per woman per year in the study group compared with .088 in the US population.⁴⁶

In contrast, a study evaluating 54 patients with CD found that the infertility rate, 12%, was similar to that in the general population. However, there was a 35% rate of spontaneous abortion in this group.⁴⁷

A European study matching 224 women with CD with 208 controls of the same age found that despite the finding that the CD patients used contraception somewhat less frequently (45% vs 50%), they were significantly more infertile ($P < .0025$).⁴⁸

Slide 33

A study by Olsen followed 343 women of reproductive age with UC who underwent IPAA. A reference cohort of 1200 women was used to establish the fecundability ratio in the general population.

The study used time to pregnancy, based on the number of periods observed, to calculate the fecundability ratio. The fecundability estimate was based only on patients whose reproductive behavior permitted conception.

The fecundability ratios before diagnosis and before colectomy were equal to or slightly higher than those of the reference population. However, the fecundability ratio for patients after the procedure was very low compared with that of the reference population.

The authors concluded that “This serious side effect must be made clear to women of reproductive age who plan to have children after surgery. We recommend that women who cannot get pregnant after surgery be referred early to a gynecologist to allow for investigations and the possibility of in vitro fertilization.”⁴⁹

Another study, of 258 women with UC who were treated with IPAA, reported that the number of births was 87% of that expected in the nonstudy population, a significant reduction ($P < .05$). Postoperatively, the birth rate was 49% of that expected, a highly significant reduction ($P < .001$).⁵⁰

Slide 34

This graph shows the cumulative incidence of pregnancy for the 4 groups in this study over a period of 5 years. The women in the “before-surgery” cohort track very closely to the reference group. About 80% of the women in the “before-diagnosis” group became pregnant in less than 12 months of trying; this level was not achieved by the “before-surgery” group or the reference group until approximately 24 months of attempting to achieve pregnancy. A reason for this difference might be that the women in the “before-diagnosis” group were younger than those in the “before-surgery” group. Median age at diagnosis of UC was 22.0 years, and median age at time of colectomy was 27.1 years.

Even after 5 years of trying, only about one third of women who had had proctocolectomies and IPAA succeeded in becoming pregnant.⁴⁹

Slide 35

Some surgical approaches may preserve women’s ability to become pregnant. The possibility that disease can be controlled medically for a sufficient period to allow the patient to become pregnant and come to term should be weighed carefully by the patient and the physician. It is desirable to minimize septic complications and the formation of adhesions, perhaps by the use of resorbable adhesion barriers such as ferric hyaluronate adhesion-prevention gel.

Some experts suggest lifting the ovaries away from the surgical field and replacing them where there is less likelihood of adhesion formation as a means of preserving ovarian function.

Laparoscopic procedures are less invasive and may cause less damage than standard procedures. The risks and benefits of any strategy must be evaluated carefully by the physician and should be shared with the patient.

Slide 36

In general, IBD has a minor impact on fertility. In CD, inflammation near the terminal ileum may affect the ovaries and cause fallopian tube blockages. The reported rates of fertility in women with CD conflict, ranging from 12% to 67%. This may be due to large-bowel involvement and proximity to the ovaries and fallopian tubes.

Some IBD medications may cause infertility in men.

More women with IBD choose not to have children because of fear, being advised not to have children, or being told that they may have more difficulty having children than would women without IBD.

Fertility can decrease significantly following IBD surgery. Clinicians should counsel their patients regarding this important side effect.

Pregnancy and Pregnancy Outcomes in Women with IBD [Slides 37-49]

Slide 37

Women with IBD are apt to have a very high level of concern for the effects of their disease on pregnancy and/or on the fetus and also for the possible effects of pregnancy on their disease.

Slide 38

The extent of the effect of IBD on pregnancy outcomes is relatively small. Areas in which the disease affects pregnancy are birth weight, gestational age at birth, and impact on spontaneous abortions.

Babies born to mothers with CD tend to be of lower-than-average birth weight. In particular, there is a difference in infants whose birth weight is below the 10th percentile ($P=.052$). This is independent of any effect that the disease might have had on maternal weight.^{51,52}

There is an increased risk of preterm birth for women with IBD. In a retrospective study of more than 300 women with IBD, the risk was greater for women with CD than for those with UC.³⁸ The same study reported an increased risk of miscarriage for women with CD but no significant increase in miscarriage for women with UC.³⁸

Overall, IBD did not have a major effect on congenital abnormalities or maternal complications.⁵¹

Slide 39

Eighteen reports on UC and 6 reports on CD are summarized. The percentage of normal births, whether full-term or premature, is the same for the 2 groups, as are the very small percentages of congenital abnormalities and stillbirths. The percentage of spontaneous abortions was slightly higher for women with CD than for those with UC; however, the therapeutic abortion rate for women with UC was nearly twice that for women with CD.⁴⁰

Slide 40

Adverse pregnancy outcomes for Swedish women with and without IBD from 1991 to 1992 were compared in this study. The adverse outcomes that carried higher risks for women with IBD were low-birth-weight infants, preterm births, and infants who were small for gestational age. The percentage of infants weighing less than 1500 grams – in other words, those in need of intensive care and at risk for respiratory distress syndrome and other conditions that threaten the lives of neonates – born to women with IBD was double that of infants born to women without IBD; however, this risk was still low. The likelihood of delivery by cesarean section was higher for women with IBD than for controls.

These figures indicate an elevated but not alarming risk to the newborn offspring of women with IBD.⁵³

Slide 41

Dominitiz and coworkers compared outcomes in a study of 746,130 single births in Washington State from 1987 to 1996. In this large sample, 262 women with IBD were identified, including 155 with CD and 107 with UC. Outcomes for infants born to

mothers with UC and those of infants born to mothers without IBD in a cross-sectional, retrospective study were compared.

The rates of adverse outcomes in this cohort were generally higher than those in the Swedish study. This is true not only for women with IBD but also for those without IBD.

More pregnancies of women with CD than with UC had adverse outcomes that were significantly different from those in the reference population. These outcomes included preterm delivery, low birth weight, and smallness for gestational age. For the most part, the differences did not indicate dire outcomes; for example, the difference in mean gestation time between women with and without IBD was less than 1 week. Both groups had significantly more cesarean sections than did the reference population.

The pregnancy outcome of greatest concern is congenital malformation. The 7.9% rate for women with UC, but not the 3.4% for women with CD, was significantly higher than the 1.7% rate in the reference population. The numbers of congenital malformations were small, making it impossible to identify any patterns. Several of the malformations were of minor importance, such as pilonidal cyst and congenital subluxation of the hip.

This finding is difficult to put into perspective, since the medical histories of the mothers were not known. Congenital malformations may result from the nutritional status of the mother, disease activity, adverse effects of therapy, or some impact of the disease process on reproductive function.⁵⁴ It is important to note that most women with UC have normal pregnancies and deliver healthy babies.

Slide 42

The bars at the left of this graph report the effect of pregnancy on UC disease activity in 528 women with inactive disease at the time of conception. These women have about 1 out of 3 chances of relapsing during the 12 months of gestation and puerperium. This is similar to the relapse rate for women with UC who are not pregnant. Thus, there is no evidence that pregnancy triggers relapse in women with inactive disease.

The bars at the right report the effect of pregnancy on UC disease activity in 227 women with active disease at the time of conception. In this group, 45% will have worsened activity, 24% will continue to have disease activity at an unchanged level, and 27% will improve. Thus, nearly three quarters of women with active disease at the time of conception will continue to have active disease at some point in their pregnancy.⁵⁵

These data suggest that for the health of both mother and baby, it is important to attempt to induce remission before conception or to wait for a period of remission before attempting to conceive. The effect of pregnancy on UC should be discussed fully by the clinician and the patient.

Slide 43

Disease activity in women with CD is compared. The bars at the left show that of 186 women with inactive disease at the time of conception, 27% experienced relapse in the period of gestation and puerperium. The first trimester and the puerperium are the most

likely times for relapse. This rate may not be appreciably different from the 12-month relapse rate of women with CD who are not pregnant.

The bars at the right show that approximately one third of women with active disease will have worsened activity, one third will continue at the same level of severity, and one third will improve.⁵⁵

Again, these data suggest that for the health of both mother and baby, it is important to attempt to induce remission before conception or to wait for a period of remission before attempting to conceive. The effect of pregnancy on both UC and CD should be discussed fully by the clinician and the patient.

Slide 44

A recent study investigated the role of human leukocyte antigen (HLA) Class II genes in IBD. Pregnant women with either UC or CD were asked to fill out questionnaires to assess whether disease symptoms improved, remained stable, or worsened. The results were correlated with mother-infant HLA disparity, based on genotyping of blood samples obtained from mother and infant. Of the 50 pregnancies studied, 46 had disparities at the DR locus, 30 had disparities at the DQ locus, and 42 had disparities at both loci. Disparity at 1 locus was not linked with any significant difference in disease score or overall disease activity either before pregnancy, during any trimester, or after delivery, but disparity at both DR and DQ was associated with significant improvement in disease score ($P=.007$) and disease activity ($P=.01$). Maternal immune response to paternal HLA antigens may play a role in pregnancy-induced IBD remission.²¹

Slide 45

Questions remain regarding the effect of pregnancy on such matters as pouch function, whether delivery should be vaginal or by cesarean section, and whether there are any unique concerns if a cesarean section is performed.

Slide 46

A retrospective survey indicated that women with IBD underwent 33% more cesarean sections than did women in the general population; this may be due to a perception that vaginal delivery poses a higher risk for women with IBD. The same study concluded, however, that women without active disease at term can safely deliver vaginally.⁵⁶ The primary risk, as observed in another study, is from episiotomy. In this survey, a substantial percentage of women, even including those who had had no previous symptoms of CD, developed perineal manifestations of CD after episiotomy. The authors suggested that mediolateral episiotomy, which involves the rectal mucosa less than does a medial episiotomy, might reduce the risk.⁵⁷

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Pouch function does not appear to be greatly affected during pregnancy or by route of delivery. In a small study of 16 pregnancies, 10 deliveries were vaginal and 6 were by C-section; there were no pouch complications.

Mean number of bowel movements per day was 8.1 during pregnancy compared with 6.5 in the postpartum period. One woman had frequent incontinence during pregnancy, and 2 had mild incontinence. One woman had nighttime incontinence postpartum.⁵⁸

Slide 48

In a recent study, questionnaires were mailed to women with UC and IPAA to evaluate pregnancy, method of delivery, and functional outcomes.⁵⁹

Of 49 deliveries among 29 respondents, 25 were vaginal and 24 were by cesarean section. In all, there were 6 pouch-related complications, 2 during pregnancy and 4 postpartum. Of the 4 pouch-related complications postpartum in the cesarean group, there were 2 women with 2 small-bowel obstructions each. The pouch-related complications during pregnancy (n=2) were probably not related to pregnancy. Most of the women experienced increases in stool frequency and in day and night incontinence during pregnancy. Prepregnancy function was regained by 83% after delivery, but 5 women – 17% – had some permanent deterioration in pouch function. Of these 5 women, 3 had vaginal delivery and 2 had cesarean sections. Multiple births and birth weight were not observed to affect postpartum pouch function.

There were no significant differences in the proportion of subjects reporting changes in stool frequency, nighttime stool frequency, or daytime and nighttime continence after vaginal delivery compared with those having a cesarean section.

Based on these results, the authors concluded that pregnancy is safe for women who have undergone IPAA and that the method of delivery does not affect pouch function.

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In summary, sexual function is often improved following surgery for UC; this may be due to improved well-being and quality of life. IPAA yields better results in terms of sexual function than does ileostomy.

It is worth noting that fertility appears to be somewhat decreased after surgery, and the potential risks should be discussed with the patient.

Overall, women with IBD do not appear to be at increased risk for complications during pregnancy or delivery.

Management of IBD in Pregnancy [Slides 50-67]

Slide 50

A total management program for women with IBD includes assessment of disease activity and choice of medical as well as surgical options, with particular attention to issues such as fertility and pregnancy. This section reviews treatment in relation to those issues.

Slide 51

A range of diagnostic modalities may be used to assess disease activity in pregnant patients with IBD. Routine laboratory values for erythrocyte sedimentation rate, hemoglobin, albumin, and C-reactive protein are vital, especially in diseases such as IBD that have an immunologic component.

Ultrasound, used to monitor the development of the fetus, is safe, and low-dose X-rays pose a minimal risk to the fetus.⁶⁰

Endoscopy is a valuable tool to assess the anatomic extent of UC.² A study reported that 38 of 41 pregnant women who had flexible sigmoidoscopies during pregnancy had healthy babies. All reported poor fetal outcomes were in high-risk pregnancies and were not temporally related to the sigmoidoscopy, suggesting that this procedure, when performed in clinically stable pregnant patients, does not frequently cause complications. However, sigmoidoscopy should be performed during pregnancy for clinically significant overt lower-gastrointestinal bleeding; diarrhea or abdominal pain are weaker indications for this procedure. Colonoscopy in pregnancy should be considered only in life-threatening disease or when the alternative is surgery.⁶¹

Slide 52

Pharmaceutical companies rarely test drugs in pregnant women⁶² and, until recently, did not routinely include women in clinical trials on the grounds that even if a woman was not pregnant at the start of the trial, it was not possible to be sure that she might not become pregnant during the trial or while the trial drug was present in her body, and the drug might cause problems with current or future pregnancies. It was also thought that hormonal cycling or other factors might affect trial results.⁶³

As a consequence, even though pharmaceutical companies now include more women in trials leading to the approval of a drug, data about a drug's effects in pregnant women and on pregnancy outcomes mostly come retrospectively after a drug has been in use for a considerable amount of time.

The standard disclaimer in prescribing information is that use in pregnancy is not recommended unless benefits justify risk to the fetus.⁶⁴

Slide 53

The FDA Use-in-Pregnancy ratings are as follows:

- A** means that controlled human studies show no risk to the fetus in any trimester
- B** indicates no evidence of risk in humans; the chance of fetal harm is remote but possible
- C** means that risk cannot be ruled out; adequate human or animal studies are lacking; the chance of fetal harm exists, but the benefits may still outweigh the risks
- D** represents positive evidence of risk, but the benefits may outweigh the risks in life-threatening situations where safer drugs are ineffective
- X** indicates that a drug is contraindicated in pregnancy⁶⁵

These ratings are subjective to the clinician's assessment of a therapy's benefits outweighing its risks. Care must be used in discussing pregnancy drug classifications with patients, as the ratings leave room for interpretation that may confuse or frustrate patients.

Slide 54

This table groups drugs currently used to treat IBD in 4 categories: those that are safe to use in pregnancy within the indications stated in the prescribing information (Category B), those that are probably safe to use, but for which data are limited (Category C), those for which there is evidence of risk but whose benefits may outweigh risks in certain situations (Category D), and those that are totally contraindicated (Category X).

When considering treatment with drugs in Category C or D, clinicians need to determine whether the benefits of drug therapy outweigh the potential risks to the mother or the fetus, bearing in mind that a disease flare due to nontreatment may also pose a risk to the mother or the fetus.

Slide 55

Sulfasalazine was the first therapeutic advance in the treatment of active UC and for the maintenance of remission in UC.⁶⁶ The drug consists of sulfapyridine linked to 5-aminosalicylic acid, or 5-ASA. It was developed for use in rheumatoid arthritis, combining the antimicrobial action of sulfonamides with the anti-inflammatory action of salicylates. The 5-ASA moiety is responsible for the anti-inflammatory activity, and the sulfapyridine moiety acts as a carrier for 5-ASA, preventing absorption in the small intestine and facilitating delivery to the colon. Most of the side effects of sulfasalazine appear to be linked with the sulfapyridine moiety.¹

Sulfasalazine and sulfapyridine cross the placenta, but no firm evidence of harmful effects to the fetus has been found, and the consensus in the literature is that it can be used by pregnant women as it is by nonpregnant women. The concentrations of the 5-ASA moiety of the drug in cord and maternal serum are lower than those of sulfasalazine because of low absorption. Concentrations of sulfasalazine in breast milk are lower than in maternal or cord serum and are not thought likely to be harmful.⁵⁵

Sulfasalazine interferes with folic acid metabolism; therefore, folate supplementation is recommended to prevent neural tube malformations such as spina bifida.⁶⁷

The clinical utility of sulfasalazine is limited by a high incidence of adverse events (headache, dyspepsia, male infertility, skin rashes), which often necessitate discontinuation of treatment or dose reduction to subtherapeutic levels.⁶⁸

Slide 56

Mesalamine is 5-ASA, the active component of sulfasalazine without the sulfapyridine moiety, to which most sulfasalazine side effects are attributed.

A prospective, controlled study was conducted of all women who contacted the Motherisk Program between 1989 and 1995 and were exposed to mesalamine during their pregnancies. The Motherisk Program is a teratogen information service in Toronto, Canada. The study enrolled 165 women, 146 of whom were exposed to mesalamine during the first trimester of their pregnancies.⁶⁹ Of these women, 56.4% had UC, and 41.2% had CD.

The mean daily dose of mesalamine in the study was lower than the dose customarily used for maintenance. Various formulations of mesalamine were taken. The largest percentage of patients took Asacol®, followed by Salofalk® and Pentasa®.

With mesalamine it is essential to take the delivery system into consideration. Without an effective delivery system, the drug is absorbed in the small intestine and not available for treatment of UC. Topical preparations of mesalamine in enema form are limited by the

extent of colon reached. Asacol® is a mesalamine tablet coated with Eudagrit®-S, a pH-sensitive polymer that delivers 5-ASA to the terminal ileum and beyond by releasing 5-ASA at pH 7 or above.⁷⁰ Salofalk®, another oral mesalamine preparation available in Canada and Europe, is coated with Eudagrit®-L, which releases at pH 6 in the proximal small bowel or jejunum.⁷¹ Pentasa® is a controlled-release mesalamine capsule that releases 5-ASA microspheres throughout the gastrointestinal tract.^{71,72}

There was no increase in the incidence of major malformations after first-trimester exposure to mesalamine compared with controls. One out of 127 mesalamine-treated women had a baby with a major malformation – an infant with an extra right thumb. In the control group, 5 of 131 mothers had infants with major birth defects – 2 with congenital dislocations of the hip, 1 with imperforated anus, 1 with aortic valve stenosis, and 1 who died at 10 weeks of age with dysplastic kidneys.

The authors concluded that the use of mesalamine in pregnancy is safe and that pregnant women with IBD should not discontinue treatment lest they experience relapses that are associated with a higher incidence of perinatal risk.⁶⁹

Slide 57

This slide summarizes the results of 2 studies of mesalamine in pregnancy. The study by Marteau compares outcomes in women taking mesalamine with those in the general population in France⁷³; the Diav-Citrin study is the Motherisk Study described previously. These studies confirm that the incidence of fetal malformations in infants born to women taking mesalamine during pregnancy is no higher than in the general population.

Slide 58

This was a small study of 19 pregnant women treated for UC with topical 5-ASA delivered by enema. All the women completed their pregnancies successfully, and there were no fetal abnormalities.⁷⁴

5-ASA enemas have been shown to be safe and effective for maintaining remission, particularly in left-sided UC, the part of the colon to which the 5-ASA enema has access. The response rate to treatment is high, and the rate of complications is low. This is particularly important in UC, because of its high rate of spontaneous relapse,⁷⁵ and equally important in pregnancy because of the threat to the fetus posed by active disease.

Slide 59

Postmarketing surveillance of ciprofloxacin use by pregnant women has failed to unearth conclusive evidence that the drug causes fetal death or congenital malformations.

In 1 report of observational cohort studies, of the 9 women who received ciprofloxacin during the first trimester of pregnancy, 5 gave birth to healthy babies. Outcomes for the remaining 4 were not attributable to ciprofloxacin. In addition, no congenital abnormalities were reported.⁷⁶

In another study, the authors concluded that the use of a quinolone (ciprofloxacin or norfloxacin) during the first trimester of pregnancy did not appear to be associated with

an increased risk of malformations or musculoskeletal problems, although there was an increased incidence of fetal distress ($P=.005$) without clear reason.⁷⁷

A third postmarketing surveillance study did not yield conclusive evidence. A spontaneous-abortion rate of 10% in 103 United Kingdom and international case reports is lower than the 20% rate for the overall United Kingdom population. Of the 8 babies born with congenital abnormalities, 3 were born to mothers who had received other drugs during pregnancy. The abnormalities noted for women who received ciprofloxacin alone were minor, and no causal relationship with ciprofloxacin has been established.⁷⁸

A meta-analysis of 7 studies of metronidazole in pregnant women failed to show an increased risk of birth defects among the infants exposed to the drug during the first trimester of pregnancy. The studies were largely with women taking metronidazole for the treatment of trichomoniasis, for which it is the drug of choice. Most of the studies reported follow-up of pregnant patients taking metronidazole but did not compare the pregnancy outcomes with those of women not taking the drug. Pregnant women clearly needing the drug should be encouraged to use it rather than go untreated, and women exposed to the drug should be reassured of the small likelihood of harm to the fetus, so that unnecessary terminations of pregnancy can be avoided.⁷⁹

Slide 60

Although there are risks associated with the use of corticosteroids in pregnancy, the risks of active disease exceed those to the fetus associated with corticosteroids. A reference guide to fetal and neonatal risk associated with drugs in pregnancy and lactation concludes that prednisone and prednisolone pose very small risks to the developing fetus and states that the American Academy of Pediatrics considers prednisone to be compatible with breast-feeding.⁸⁰

Although corticosteroids are known to be effective for induction of remission of moderate to severe CD, these agents have not been shown to be effective for long-term maintenance of remission. Corticosteroids also have important systemic side effects, some of which are irreversible. Thus, it is evident that these agents should be used with caution.^{1,81,82}

Slide 61

AZA and its active metabolite, 6-MP, are common choices for maintenance therapy in IBD after other agents have been used to induce remission or for patients who have not responded to systemic steroids.^{1,83} AZA is also used, often with prednisone, by transplant patients.⁸⁴ A review of pregnancy in women with renal allografts reported no frequent or predominant developmental fetal abnormalities. Those that were reported were rare and often resolved.⁸⁵ A small study of women with IBD taking AZA reported no congenital abnormalities and no perinatal problems. The authors concluded that AZA is safe in pregnancy for patients with IBD and that termination of pregnancy is not mandatory for patients who conceive while taking the drug.⁸⁶

A recent, large study assessed outcomes of infants born to 79 mothers with IBD who took AZA/6-MP either before conception, before conception and during pregnancy, or just during pregnancy or to 76 fathers who had been treated before conception.⁸⁷ Results

indicated no significant difference in rates of miscarriage, congenital abnormalities, premature birth, or neonatal and childhood infection between the treated cohort and untreated controls.

In another study, semen quality and, thus, fertility in men with IBD was not reduced by treatment with AZA.¹³

AZA has been found to be relatively safe in pregnancy. In a surveillance study of more than 225,000 pregnancies, no major malformations were observed in 6 categories – cardiovascular defects, oral cleft, spina bifida, polydactyl, limb reduction defect, and hypospadias.⁸⁰ Fetal immunosuppression has been observed, including bone marrow suppression, leukopenia, and thrombocytopenia.⁸⁶ Overall, the risk of a disease flare-up may strongly outweigh the risk of fetal damage, and this issue should be decided by patient and physician in each case.⁴

Slide 62

There are relatively little data on the safety of cyclosporine in pregnancy; however, based on the data available, it does not appear that cyclosporine poses a major risk to the fetus. The drug is not teratogenic in animals, and it is not likely to be teratogenic in humans. There is a fairly high incidence of fetal growth retardation and low-birth-weight infants.

The National Transplantation Registry was established to study outcomes in all solid organ transplant recipients. The majority of the experience has been derived from female renal transplant recipients. Outcomes showed that no specific congenital abnormalities or birth defects were associated with cyclosporine use. Of the live-born infants, 56% were premature and 49.5% had low birth weight.⁸⁸

In a small report,⁸⁹ the safety of cyclosporine was examined in 5 pregnant women who received the drug during their pregnancy. Four of 5 pregnancies resulted in live births and 1 had a missed abortion at 8 weeks. No congenital abnormalities or developmental defects were observed.

A recent, small study found that patients given cyclosporine in combination with steroids for severe colitis tended to deliver lower-birth-weight, premature babies; overall, pregnancy outcomes were comparable to those for an untreated IBD control group.⁹⁰

If cyclosporine is used during pregnancy, it should be administered and monitored at experienced IBD centers.²

Slide 63

Infliximab is a monoclonal antibody active against tumor necrosis factor alpha, which has various roles in disease pathogenesis beyond its proinflammatory properties⁹¹; including in the initiation and propagation of CD.

In 54 known outcomes of pregnancies in 102 women exposed to infliximab, there were 10 spontaneous abortions, 8 therapeutic abortions, 1 preterm infant, and 1 congenital malformation.⁴¹

It is not possible to determine with confidence whether these outcomes were due to the drug or to the underlying disease. Infliximab has not been found in breast milk.⁹²

Slide 64

Methotrexate is contraindicated during pregnancy and for breast-feeding mothers. Forty-five women who became pregnant after discontinuing treatment with methotrexate (mean interval 2.7 years) had 31 live births, 7 spontaneous abortions, and 7 elective abortions.⁸⁰

In addition, of 10 pregnancies in women exposed to methotrexate, a folic acid antagonist, during the first trimester, 3 resulted in malformed infants. The pattern of methotrexate-related congenital abnormalities is similar to that caused by another folic acid antagonist, aminopterin.⁸⁰

In men, methotrexate appears to cause oligospermia, which resolves after the drug is discontinued; long-term effects are unknown.⁸⁰

Slide 65

The drugs most likely to be safe during pregnancy are sulfasalazine, mesalamine, and corticosteroids. Both sulfasalazine and corticosteroids have a fairly high rate of side effects, although these are not likely to affect fetuses.

Among the immunosuppressive agents, AZA and 6-MP appear to be safe in pregnancy. Cyclosporine is contraindicated during breast-feeding, and methotrexate is contraindicated during both pregnancy and breast-feeding.⁸⁰

Of the antibiotics, ampicillin and the cephalosporins are safe. Ciprofloxacin and metronidazole are probably safe, although the data are far from unequivocal. Ciprofloxacin does not appear to be linked with an increased risk of major congenital malformations,^{78,80} but it is not recommended for women who are breast-feeding.⁸⁰ Women who have been exposed to metronidazole during pregnancy should be reassured that the drug is probably safe and should not be counseled to terminate their pregnancies.⁷⁹

Slide 66

This slide groups IBD drugs into 3 categories: those that are safe during breast-feeding, those that are contraindicated, and those for which sufficient data are lacking.

Those that are safe include both oral and topical mesalamine, sulfasalazine, and corticosteroids.

Methotrexate, metronidazole, ciprofloxacin, and cyclosporine are contraindicated.

For AZA/6-MP, infliximab, and tacrolimus, there are limited data available for a strong recommendation.

Slide 67

Once again, pregnancy outcomes are best when the patient is in remission at the time of conception. The most important factor in the course of the pregnancy is the health of the mother. Patients should be encouraged to remain adherent to their therapy through their

pregnancies, since the risk of relapse is a greater threat to mother and infant than the risk from most drugs used to treat IBD.

Many of the IBD drugs appear to be safe in pregnancy. Some drugs have an effect on fetal growth; therefore, monitoring fetal growth is particularly important. Some nutritional supplementation may be necessary.

Menopause in Women with IBD [Slides 68-73]

Slide 68

Menopause, with its important hormonal changes, requires special attention in women with IBD, with regard to the physiologic effects of these changes on the disease process and with regard to treatment.

Slide 69

A woman is born with a finite number of follicles. As this number declines below a certain point, smaller amounts of estradiol are produced. Natural menopause can take place as early as the 40s and as late as the late 50s; the average age is 51 years.⁹³ Oophorectomy will cause menopause at whatever age it is performed.

The most prominent hormonal changes are a steep decline in estradiol concentrations, from as high as 100 pg/dL (premenopause) to 20 pg/dL or lower (postmenopause). Estrone, an oxidation product of estradiol, is the main circulating hormone. Testosterone, the main ovarian androgen, also declines.

There are no data currently available on the effect of menopause on IBD.

Slide 70

There has been much discussion of menopause as a natural process to which women should adapt “gracefully.” This point of view overlooks that fact that menopause brings physiologic changes, some of which are clearly detrimental to a woman’s health.

Bone loss and a decrease in bone mineral density (BMD) often lead to osteoporosis and risk of serious fractures that limit physical activity and may shorten life. Because CD already carries some risk of bone loss, this is of particular concern for women with CD. Women with CD are known to experience a more rapid reduction in BMD. A complete explanation for this phenomenon is lacking; however, several factors are implicated. These include malabsorption of vitamin D due to small-bowel involvement or ileal resection, the direct effects of inflammatory cytokines, and systemic corticosteroid therapy. Bone loss due to systemic steroid therapy is well documented, and many women with CD become steroid dependent.⁹⁴

A majority of women may experience vasomotor symptoms, including “hot flashes.”

Adverse changes in lipid balance increase the risk of cardiovascular disease. Prior to menopause, women are at lower risk for cardiovascular diseases than are men; however, by age 75, the risk levels for women and men are the same. Much of the increase in cardiovascular risk may be attributed to increasing lipids, particularly low-density lipoprotein cholesterol.

Diminishing levels of estradiol may also bring about a number of urogenital symptoms, such as vaginal dryness, pain during intercourse, urinary incontinence, and an increase in risk for urinary tract infections.

Slide 71

Hormone replacement therapy, or HRT, is drug therapy that replaces estrogen and other hormones in the patient who has passed menopause, whether natural, as the ovarian reservoir of follicles becomes exhausted, or surgical, through removal of the ovaries.

Estrogen replacement was first approved for managing menopausal symptoms 60 years ago. The symptoms that women and their physicians were concerned about were those categorized as “vasomotor symptoms,” principally hot flashes and night sweats that many women found to be genuinely incapacitating. Estrogen replacement was also prescribed as a way for women to slow changes in body morphology and maintain sexual attractiveness.

In the mid 1970s, estrogen was found to increase the risk of endometrial cancer. Unopposed estrogen – that is, estrogen without progestin – is now prescribed only for women who have undergone surgical removal of the uterus.

Since the 1980s, HRT formulations for women with intact uteri contain both estrogen, frequently in the form of estradiol, and some form of progestin, which has been found to decrease the risk of endometrial cancer. The estrogen levels in current HRT formulations are also lower than those given previously.

In 2002, the estrogen/progestin arm of the large Women’s Health Initiative was halted, because women using combination HRT were experiencing a larger-than-expected number of heart attacks, blood clots, and strokes, and their risk of invasive breast cancer was also higher than anticipated. The risks of this therapy were observed to outweigh its benefits.⁹⁵

Slide 72

In addition to improvement in vasomotor symptoms and slowing the changes in body morphology such as thinning of the epidermis and vaginal dryness, other benefits have been demonstrated to derive from HRT.

Perhaps the most important benefit from the standpoint of women with IBD, especially those with CD, is that HRT reduces loss in BMD and the incidence of osteoporotic fractures. A 2-year prospective study of HRT in postmenopausal women with UC or CD demonstrated that HRT significantly improved both radial and spinal bone density.⁹⁶

HRT formulations also have an effect, generally beneficial, on lipid balance. The specific changes in the lipid fractions vary with individual HRT formulations.

It would logically follow that improvements in lipid balance would lead to a reduction in coronary artery disease – CAD – and increased life expectancy. In fact, a very large retrospective study published in 1991, the Nurses’ Health Study, followed several thousand women over a 10-year period and demonstrated that those taking HRT did

indeed have a lower rate of CAD.⁹⁷ However, the study has been criticized on the grounds that the women in the HRT cohort were more highly educated than those not taking HRT and were thus likely to adopt a healthier lifestyle. Much smaller subsequent studies in women at higher risk, such as those with established CAD, have failed to show any benefit.

The risks of HRT are now thought to potentially outweigh the benefits. In the recently stopped combined-therapy arm of the Women's Health Initiative, the risks of invasive breast cancer and cardiovascular disease, or CVD, appeared to increase with long-term therapy. Some women may not feel that the benefits of HRT are worth the risks, especially since alternatives are available.⁹⁸

Slide 73

The recommendation that all women with IBD should *consider* HRT does not mean that all or most women should receive HRT. The patient and her physician should evaluate the severity of symptoms and her capacity to tolerate them as well as the feasibility of using alternate therapies.

Individualization of therapy means, for example, that the residual level of estrogen needs to be assessed; not every woman needs the same amount of estrogen replacement. The extent of bone loss needs to be measured carefully with dual-energy X-ray absorptiometry, or DEXA.

The risk/benefit evaluation takes many factors into consideration. Women with osteopenia or osteoporosis face genuinely severe health outcomes, which include incapacitating fractures, dependency, and nursing home confinement. The benefits of HRT for these women may outweigh the risks. On the other hand, for women at increased risk for breast cancer, the risks of HRT may outweigh the benefits.

Cardiovascular risks or benefits associated with HRT are controversial. Minimally, HRT is not indicated as a cholesterol-lowering drug or as cardioprotective therapy. For women with overt dyslipidemia at the time of menopause, a range of effective lipid-lowering drugs are available.

Osteoporosis in IBD [Slides 74-83]

Slide 74

Osteoporosis and osteopenia are common in patients with IBD. Corticosteroids contribute to these conditions, but bone loss leading to osteoporosis and the likelihood of sustaining fractures and losing the capacity to live independently may affect IBD patients whether or not they are treated with corticosteroids.^{99,100}

Slide 75

Risk factors for osteoporosis in the general population include age, being white or of Asian descent, physical inactivity, and being small and thin. Other risk factors include premature loss of gonadal function – either ovarian or testicular – and nulliparity.¹⁰⁰

The impact of osteoporosis is severe, particularly for women. Based on a population-analysis model, it is estimated that 54% of 50-year-old women will sustain osteoporosis-related fractures during their remaining lifetimes. For a woman at this age, the lifetime

probability of sustaining a hip fracture is 18.4%, a vertebral fracture 35.3%, and a Colles fracture 17.3%. The consequences are that 6.7% of women who experience such fractures will decline to dependent status, and a fracture will result in nursing home placement for 7.8%.⁹⁹

Slide 76

Risks of osteoporosis that affect IBD patients over and above those that affect the general population include low bone mass, calcium malabsorption, and the effects of drug therapy.¹⁰¹⁻¹⁰³

In a study of 61 patients with IBD, 23% had BMD levels more than 2 standard deviations (SDs) below those of controls. In this study, 16 of 23 patients who had never been treated with corticosteroids nonetheless had osteopenia. One of 6 newly diagnosed patients with UC and 6 of 8 newly diagnosed CD patients had osteopenia.¹⁰⁰

The inflammatory process in IBD triggers an increase in inflammatory cytokines (interleukins, tumor necrosis factor) within the bone marrow environment, resulting in increased bone resorption. Patients with CD are commonly deficient in vitamin D because of reduced intake of supplemented food products as well as reduced absorption in the small intestine. In the United Kingdom, this deficiency affects 30% of CD patients and 62% of those with small-bowel resections.¹⁰⁰

Several drugs contribute to osteopenia and osteoporosis. Corticosteroids cause not only enhanced bone resorption but reduced bone formation as well.¹⁰⁰

Slide 77

The high rate of osteopenia and osteoporosis in patients with IBD calls for active and prompt intervention to prevent further bone loss and preserve bone mass.

Measurement of bone density should be obtained for all patients with IBD to establish a baseline and to assess current status. The method of choice is DEXA, which is a sensitive, good predictor of fracture risk and exposes the patient to a much smaller dose of radiation than does a conventional X-ray. Assessment of vitamin D adequacy is necessary for all patients with CD, malnourished patients, or those with small-bowel resection.

Other preventive steps include weight-bearing physical activity, calcium supplementation, cessation of smoking and excess alcohol consumption, and HRT for postmenopausal women or for men with hypogonadal function.

Patients whose osteoporosis is established, those who do not want to incur the risks of HRT, and those who have continued decline in BMD should be treated with calcitonin or bisphosphonates.¹⁰⁰ Parathyroid hormone, or PTH, self-administered in daily injections, is under study and has shown promising results to date in decreasing the risk of vertebral fracture and increasing spinal bone density in postmenopausal and glucocorticoid-induced osteoporosis; however, it also decreases radial bone density, and its long-term safety and efficacy are not yet known.¹⁰⁴

Slide 78

Bone loss induced by corticosteroids takes place rapidly, during the first few weeks or months of treatment. In 1 study, patients on long-term low-dose prednisone lost BMD in the spine at the rate of 2% per year.¹⁰⁰ Bone loss is dependent on duration of corticosteroid exposure, total cumulative dose, and dosage level. Many clinicians recommend prophylaxis with calcium supplementation and small doses of vitamin D upon initiation of steroids for active IBD.

Corticosteroid-induced bone loss has been shown to increase the risk of fractures. A retrospective cohort study in the United Kingdom followed nearly 250,000 patients to whom oral corticosteroids had been prescribed for a mean period of 1.3 years. The rate of hip fractures was increased by 77% in those taking daily doses of 2.5 to 7.5 mg, and by 127% in those taking higher doses.¹⁰⁵

Slide 79

The continuous process of bone remodeling consists of a resorption phase and a formation phase, both of which are affected by systemic corticosteroids. Bone resorption is carried out through the activity of osteoclasts. It has been suggested that corticosteroid-stimulated parathyroid release can increase the bone-resorption activity of osteoclasts. Bone formation is carried out by osteoblasts, whose formation and proliferation is directly inhibited by corticosteroids. At the same time, corticosteroid therapy is also linked with calcium malabsorption, increased renal calcium excretion, and inhibition of sex hormone secretion, which may lead to bone loss.¹⁰⁶ Osteoblast and osteocyte apoptosis have also been proposed as factors in corticosteroid-linked bone loss.¹⁰⁵

Budesonide is a corticosteroid with possible advantages over prednisone in that it combines a high degree of topical activity with low systemic activity. It provides improvement to patients with active CD without the side effects experienced by patients taking prednisone. Budesonide prolongs clinical remission in CD patients, although response is not maintained at 1-year follow-up. Short-term budesonide does not suppress osteoblast activity, as does prednisone; however, the long-term effects of budesonide on BMD are not known.⁹⁴

Slide 80

This table shows the recommended interventions for 3 groups of patients at risk for corticosteroid-induced osteoporosis. They are divided based on their T scores on DEXA scans. A T score less than 1 SD lower than the mean bone mass of a young-adult reference population is considered normal. A T score between 1 and 2.5 SDs lower than in the reference population indicates osteopenia; more than 2.5 SDs indicates osteoporosis.

Risk-factor modification – for instance, smoking cessation, reducing alcohol consumption, and weight-bearing exercise – as well as calcium and vitamin D supplementation is recommended for all women.

Bisphosphonates are prescribed for patients with osteopenia and osteoporosis. General guidelines include a urinary N-telopeptide assay, which is a specific marker for osteoclastic activity, as well as measures such as weight-bearing exercise, smoking

cessation, and alcohol reduction. Hydrochlorothiazide also may help by increasing intestinal calcium absorption and decreasing urinary calcium excretion.¹⁰⁰

Selective estrogen receptor modulators, specifically raloxifene, may be effective in preventing fractures; however, these drugs can cause reactions similar to menopausal symptoms.¹⁰⁷

Slide 81

Risedronate is a new pyriminyl bisphosphonate active in preventing bone resorption. It has been studied for prevention of bone loss in patients taking concomitant corticosteroid therapy. The graph at the left shows results after 12 months of treatment in a prevention study. Patients taking risedronate did not experience any significant change in BMD at the lumbar spine, whereas placebo-treated patients sustained a significant decline. Significant treatment benefits were seen at several sites including the lumbar spine, the femoral neck, and the trochanter of the hip.¹⁰⁶

The graph at the right shows the difference between patients taking risedronate and those taking placebo after 12 months in a study with high doses of corticosteroids. There were significant gains in BMD by patients treated with risedronate.¹⁰⁸

Risedronate therapy has been demonstrated to prevent bone loss in patients starting corticosteroid therapy as well as to increase BMD in patients taking high doses of oral corticosteroids.^{106,108}

Slide 82

In a prospective study enrolling 38 patients with CD who were taking corticosteroids, serums were analyzed for surrogate markers of bone turnover at baseline and 4 weeks after the patients received infliximab. The patients had significant decreases in Crohn's Disease Activity Index (CDAI) scores and in corticosteroid doses. The investigators also observed significant increases in bone alkaline phosphatase, a marker for bone synthesis, and no change in N-telopeptide of type I collagen, a marker for bone resorption.

The researchers concluded that for patients with CD taking corticosteroids, infliximab can increase bone synthesis without increasing resorption; they also postulated a potential beneficial effect on CD activity, which would explain the reduction in need for corticosteroid therapy.¹⁰⁹

Slide 83

Osteoporosis, widespread in the general population, is of special concern for persons with IBD. The risk factors for osteoporosis are so common that the individual with no risk factors would be the exception rather than the rule – for example, a young, active, nonsmoking man who consumes moderate amounts of alcohol, has a robust physique and adequate calcium intake, and is neither white nor Asian in ethnicity would appear to have no risk factors for osteoporosis. All others have some risk factors.

To the common risk factors must be added those that come with IBD, especially with CD – poor absorption of calcium and other nutrients and disease-related inflammatory processes that favor bone loss. Finally, corticosteroids, which are useful drugs, especially in CD, contribute to loss of bone mass.

The consequences of losing bone mass are well known – increased risk of fractures, loss of mobility and capacity for independent living, and possible premature mortality. These severe consequences, coupled with the understanding that bone loss can begin early in the disease course and also early after initiation of steroid therapy, make a strong case for using active measures to preserve bone mass. These begin with monitoring, preferably by DEXA with other laboratory tests for calcium loss. Wherever possible, risk factors should be modified. Finally, some drugs such as calcitonin and bisphosphonates have been shown to preserve bone mass.

Clinical Management and Adherence Issues in IBD [Slides 84-93]

Slide 84

Adherence to treatment can make the difference between a successful outcome and treatment failure. Several categories of factors affect adherence – those related to the disease itself, those related to treatment, and patient-related variables. Optimizing adherence is a major goal in the management of IBD.

Slide 85

Patients are more likely to adhere to treatment regimens for the immediate relief of symptoms than for long-term management of a disease process. In IBD, patients take their medications as prescribed when disease is severe, when flares are frequent and intense, and when they experience severe complications. Once remission has been attained and symptoms subside, they are more likely to stop taking their medications.

The reasons for this are numerous: When symptoms are in remission, patients may believe they are cured and no longer need their medications; they may not understand the need to maintain remission, and they may simply get tired of the medication regime.¹¹⁰

Slide 86

Numerous factors related to the treatment regimen affect adherence. The more times per day a medication needs to be taken, the more likely it is that the patient will miss one or more doses; a once-daily dosing schedule is the easiest for the patient to maintain. The oral route is preferred over all others, and the pill or tablet should not be too difficult to swallow; some patients are simply unable to swallow unusually large pills.

Economic issues are clearly a factor, especially when patients do not have insurance that includes a prescription plan. Studies have shown that as many as 15% of patients do not fill prescriptions initially. The cost may be a reason, particularly for patients with comorbid conditions who are taking multiple medications.

Some drugs used in IBD pose larger adherence problems. With sulfasalazine or corticosteroids, there is a need to manage side effects in order to maximize adherence.

Mesalamine's side-effect profile and dosing may encourage adherence. Efficacy is dose related, but there is no accompanying dose-related toxicity, and there is no need to start with low doses and titrate upward. The same dosage is used for induction of remission as for maintenance of remission – a regimen that is less confusing to the patient.¹¹⁰

Slide 87

Ultimately, it is the patient who will or will not adhere to the treatment regimen. An inadequate education¹¹¹ and inadequate ability to follow a treatment regimen¹¹² are factors that have been found to decrease patient adherence. If the patient understands the need to treat the disease – in other words, that it will not go away by itself – and also understands that the proposed treatment regimen, if followed carefully, will lead to important improvement in the way she feels, she is more likely to adhere to treatment. Unfortunately, the uncertain nature of IBD and the adverse effects that some medications produce reduce many patients' confidence in the efficacy and safety of the treatment regimen.^{9,110}

Treatment needs to be individualized to the patient, and some patients, such as those with psychiatric disorders¹¹³ or younger, unmarried men, will pose greater adherence problems than others.¹¹⁴⁻¹¹⁶

In addition, there are some specific patterns of nonadherence. Patients may not fill a prescription to begin with or may fail to refill it. They may forget or skip doses or exceed the prescribed dose on the theory that “if a little is good, more must be better.” They may take the medication at incorrect intervals, such that the desirable steady-state serum level is not achieved; and they may administer the medication incorrectly, as with drugs that are to be taken via enema.¹¹⁰

Slide 88

The rate of nonadherence to medication regimens for illnesses other than IBD has been estimated to be as high as 50%.¹¹⁷ Compliance studies with sulfasalazine reported that just 4 weeks after hospital discharge, 41% of patients with quiescent UC had subtherapeutic levels of sulfasalazine's metabolite, sulfapyridine, indicating that these patients had not continued to take their medication as prescribed.¹¹⁸

The rate of adherence in clinical trials is thought to be higher than that in community practice. Trials are generally of relatively short duration; patients who enroll in trials may be more motivated to adhere to treatment; and monitoring of patients in clinical trials may reinforce adherence. Thus, the adherence rates in clinical trials do not reflect the extent of the problem.¹¹⁰

Slide 89

This graph shows the results of a study of the relationship between adherence to the medication regimen and clinical recurrence in a cohort of patients with UC in remission. At 6 months, 12 patients had sustained recurrences. All 12 patients had documented compliance below 75%. The median amount of medication taken by the nonadherent patients was 26% of that prescribed, whereas the patients in full remission took 83% of their medications. The difference was significant. At 12 months, another 19 patients had recurrences. Of these, 15 were found to be nonadherent. In total, 27 (87%) of 31 patients who relapsed were nonadherent, compared with 18 (26%) of 67 remaining in remission.¹¹⁹

Slide 90

Patient education may be the crucial element in reinforcing adherence to treatment and thereby improving outcomes. Patients need to understand that IBD is a chronic, lifelong

illness. It may vary in symptom severity, but it will never disappear entirely. There may be long periods of remission, but patients need to know that a relapse is always possible.

Therefore, the goal of a treatment plan needs to be 2-fold: first induce remission, then maintain remission. The second goal, and the treatment plan that supports it, is at least as important as the first goal.

For these goals to be achieved there needs to be a reciprocal relationship between the patient and the physician rather than the old-style paternalistic relationship in which the patient is simply expected to follow doctor's orders without question.¹¹⁰

Involvement of family members is an important part of reinforcing patient adherence. Family members can be strong supporters of the treatment plan if they fully understand its importance. On the other hand, if they do not understand the objectives of the treatment plan, they may be detractors; for example, "You seem to be much better; why do you have to keep taking that medicine?"

The treatment regimen needs to fit with the individual patient's daily life. Patients may be unwilling to take medication at work or at school. Rather than mandating a dosing schedule that the patient is likely to ignore, it is better to adapt the dosing schedule to her needs. She is more likely to keep to a simple regimen than a more complex one.

IBD is an emotionally debilitating disease, especially for women. In addition to the physical symptoms, a host of concerns affect patients, leaving few parts of their lives untouched. Emotional and psychological support will give the patient greater motivation to stay with the treatment plan.

Finally, rather than simply handing the treatment plan to the patient, the physician needs to get her "buy-in" to the therapeutic goals. A patient who is committed to the goals of the treatment plan is more likely to achieve a better outcome.¹¹⁰

Slide 91

A study enrolling 203 patients with UC receiving treatment in the gastroenterology departments of 4 hospitals in the United Kingdom evaluated the effectiveness of a patient-centered approach to management of UC. Patients were randomly assigned to an intervention group (n=101) or a control group (n=102). Intervention and control patients were matched for age, sex, time since diagnosis, and extent of disease, and equal numbers from each hospital were assigned to each group. Median duration of follow-up was 14 months.

Patients in the intervention group collaborated with a clinician to develop personalized self-management regimens and were offered direct access to outpatient services on request. Every patient in the intervention group had a 15- to 30-minute consultation with a clinician, which resulted in a personalized guided self-management regimen being developed for each patient. The objective of the regimen was that patients would recognize symptoms of a relapse and agree on a protocol, including drugs and dosages,

for use in the event of relapse. Copies of the self-management regimen were provided to each patient's primary care physician.

The assumption of the study was that this method of management would be acceptable to patients, result in a clinically worthwhile reduction in the delay between onset of symptoms and treatment, and reduce outpatient attendance without an accompanying decline in health-related quality of life.¹²⁰

Slide 92

This graph shows mean time to relapse treatment for the 2 groups. Relapses were treated earlier in the intervention group than in controls. Time to treatment after relapse was 14.8 hours compared with 49.6 hours in the control group, a highly significant difference of 34.8 hours ($P < .0001$). In the intervention group, treatment started within 2 days for 97% of relapses, whereas in the control group, this took place for only 63% of relapses.¹²⁰

Other important differences between the intervention group and the control group were with regard to outpatient visits and time spent visiting physicians. During the trial period, patients in the intervention group made 0.9 outpatient visits per patient-year, compared with 2.9 in the control group, a highly significant difference ($P < .0001$). Control patients also spent more than 6 times longer visiting physicians – 6.2 hours versus 1 hour ($P < .0001$). The control group made 297 clinic visits and missed 47 appointments, compared with 88 clinic visits and 1 missed appointment in the intervention group. These differences also had considerable economic impact; control group patients spent approximately 10 times the amount in travel costs to and from the clinic.¹²⁰

Slide 93

Although the difference between the number of relapses in the 2 groups was not significant, there was a trend in favor of the intervention group; mean number of relapses in the intervention group was 1.53 versus 1.93 in the control group. Similarly, there was a trend in favor of the intervention group with regard to duration of relapse if treatment was initiated in the first 24 hours: 17.7 ± 17.1 days versus 25.5 ± 37.4 days.

At the end of the trial, patients in the intervention group were asked if they wanted to continue with the self-management regimen or return to the original one; 82% of patients preferred the new system, and 2% preferred the old system. Ninety-five percent of control patients also decided to adopt the self-management system.

At the start of the trial, clinicians had doubts; they were concerned about the possibility of increased demand on consultation time, and they were not confident that patients would treat themselves appropriately. At the end of the trial, all clinicians acknowledged that the intervention had been successful and indicated that they would incorporate the self-management approach into their own practices.¹²⁰

General Conclusions: Special Considerations for Women with IBD [Slides 94-97]

Slide 94

Although the incidence of IBD is approximately the same in the 2 sexes, women are affected more severely, with regard both to symptom severity and to the number and intensity of concerns about the disease and its effects on their lives. Men and women share concerns about disease progression and the effects of disease on daily living;

however, women have greater concerns about body image, attractiveness, sexual activity, and the effects of disease and treatment on fertility and pregnancy.

The normal discomforts associated with the menstrual cycle may be exacerbated for women with IBD, and there are indications that OCs may be related to flares in disease activity. The change in OC formulations may have eased this problem to some extent, but women with IBD may want to consider alternative methods of contraception.

Surgery, in particular IPAA, usually results in important improvements in quality of life, since it allows for a natural means of defecation without the need for a stoma or an external device. The benefits to quality of life from ileostomy are fewer; many women feel decreased attractiveness, in particular because of the need for an external appliance. Overall, most women who have surgery do find that there is postoperative improvement in sexual activity.

Slide 95

The data on fertility in women with IBD are on the whole very positive. Various studies have put the fertility rate for both UC and CD at or near 90%, although there is some indication that fertility may be affected in women with CD because of pelvic inflammation blocking fallopian tubes.^{37,40}

Fertility in women who have had IPAA is drastically reduced, to as low as 20% of normal.⁴⁹

Voluntary childlessness is high in both UC and CD and to some extent makes the fertility data difficult to interpret.

The data on pregnancy outcomes in women with IBD are positive. The disease has minimal impact on pregnancy outcomes in terms of percentage of newborns with congenital abnormalities. There is an increase in spontaneous abortions in women with CD. Newborns may be of below-average birth weight, and there is an increased risk of preterm birth.

There are some effects of pregnancy on disease activity such that conception during a period of remission is preferable to conception during active disease.

Some IBD drugs are known to be safe during pregnancy – mesalamine, sulfasalazine, and some antibiotics. Methotrexate and thalidomide are contraindicated. The data on other drugs, including corticosteroids, cyclosporine, and AZA/6-MP, are subject to interpretation; risks should be weighed against benefit.

Overall, disease activity is a greater threat to pregnancy than treatment is.^{20,121}

Slide 96

Menopause, especially in women with CD, brings an aggravated risk of bone loss potentially resulting in osteopenia and osteoporosis. Corticosteroid use adds another element of risk.

In addition to the well-known vasomotor symptoms, menopause also brings with it an increased risk of CVD due to hormonally related changes in lipid balance. By age 75, a woman's cardiovascular risk is equal to a man's.

The benefits of HRT for cardiovascular risk reduction are controversial. Lipid balances tend to improve, but a survival benefit has yet to be convincingly demonstrated, and increased risks of breast cancer and cerebrovascular accidents may offset any benefit.

Because of the high risk of osteoporosis in postmenopausal women, particularly those with CD who have been treated with steroids, it is vital to institute an active plan to preserve bone mass. This would include regular monitoring of BMD, preferably with DEXA, modification of risk factors such as smoking and excessive alcohol use, an exercise program, and treatments that preserve bone mass such as calcium and vitamin D supplementation, or drugs such as calcitonin and bisphosphonates.

Slide 97

For clinical management of IBD to be successful, the patient must adhere to the treatment. Adherence is affected by a great many factors relating to the disease itself, the treatment plan, and the patient's understanding of her disease.

Adherence is strongly associated with good treatment outcomes, and, conversely, nonadherence is associated with relapse. Accordingly, the patient needs to understand that IBD is a chronic, life-long disease and that the goals of therapy are always 2-fold – to achieve and then to maintain remission. Adherence during remission is more likely to decline, as the patient loses the sense of urgency about taking medication.

To be successful, any treatment plan must dovetail with the patient's life and needs. Finally, communication between the physician and the patient must go both ways. The patient is less likely to adhere to a treatment regimen that is presented to her under the heading of "doctor's orders" and much more likely to adhere to a plan if she has had input, understands the goals, and has made a commitment to the particulars of the plan.