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Review Article

Optimizing the Care and Health of Women with Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) including both ulcerative colitis and Crohn's disease is increasing worldwide. Although diagnosis is equally found in men and women, the chronicity of IBD poses a unique impact on the milestones of a woman's life. As the gastroenterologist becomes increasingly important in the health maintenance of patients with IBD, this review stresses the unique gender issues in women with IBD related to menstruation, cervical cancer, sexual health, contraception, and menopause that may affect the course of disease, treatment decisions, and quality of life.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory bowel disease which includes both ulcerative colitis (UC) and Crohn's disease (CD) [1, 2]. The two diseases are both inflammatory conditions but present very differently and involve different parts of the gastrointestinal tract. UC was first described by Wilks in the 1800s [3]. It is an inflammatory disease that is characterized by continuous inflammation of the colonic mucosa that extends proximally from the rectum [1]. The natural history of the disease ranges from periods of quiescent remission to flares. The mainstay of treatment is pharmacologic therapy. However, up to 30% of individuals will necessitate total proctocolectomy due to refractory disease, dysplasia, or the development of cancer [4, 5]. The standard surgical options include total proctocolectomy and end-ileostomy, proctocolectomy with ileoanal pouch anastomosis (IPAA), and, less frequently recommended, abdominal colectomy with ileorectal anastomosis [4]. Crohn's disease was first reported by Crohn et al. in 1932 [6]. It can involve any portion of the gastrointestinal tract from mouth to anus. It is classically characterized by skip lesions in which there are discrete areas of diseased bowel separated by normal bowel and typically it spares the rectum [2]. Approximately 50% of patients have their disease involving the terminal ileum and colon, 30% have isolated small bowel disease, 20% have isolated colonic disease, and up to 25% will also have perianal complications [2]. Crohn's disease can present in many different ways often based on the underlying disease phenotype. The three classic types of Crohn's disease include inflammatory disease (nonpenetrating and nonstricturing), stricturing disease, and fistulizing disease. Similar to UC, the natural history of disease varies between remission and flares. The mainstay of therapy is pharmacologic management of disease [2]. However, surgery will be necessary in up to 80% of individuals with 50% undergoing a surgery within 10 years from their diagnosis [5, 7]. Unlike UC, the surgical management of Crohn's disease is not curative. Therefore, the types of surgery are dictated by the presenting problem (e.g., stricture or fistula) and a goal of removing the smallest amount of bowel necessary.

Both CD and UC are increasing in prevalence globally with as many as 1.4 million individuals in the United States and 2.2 million individuals throughout Europe [8, 9]. The overall incidence of IBD in pediatrics is rising worldwide. Benchimol et al. reviewed 139 studies from 32 different countries from 1950 to 2009 to assess the worldwide epidemiology of childhood-onset IBD. They noted that, in studies reporting statistical trends, there has been a 60% increase in childhood onset Crohn's disease and 20% increase in UC [10]. Similarly,

the incidence of IBD in adults is also rising globally with the highest prevalence in Europe and North America [11]. The peak incidence of IBD is between 15 and 30 years old [12]. IBD affects men and women equally. An important difference between pediatric onset and adult onset IBD is that pediatric onset IBD is associated with more extensive intestinal involvement and a more rapid progression of their disease [13, 14].

However, because IBD is a chronic illness, the impact of IBD on women is unique. IBD may affect the major milestones of a woman's life including menstruation, sexuality, family planning, and menopause. Rarely discussed topics such as how medications and surgery may adversely affect self-image are critical to broach with patient. As the gastroenterologist becomes increasingly important in the health maintenance of patients with IBD, this review seeks to stress the unique gender issues in women with IBD related to menstruation, cervical cancer, sexual health, contraception, and menopause that may affect the course of disease, treatment decisions, and the quality of life.

2. Body

2.1. Quality of Life. The overall reported quality of life (QOL) with IBD is variable and is often dependent on symptom severity [15, 16]. Often, CD is reported to have a greater negative impact on QOL compared to UC [16]. One challenge affecting the overall QOL is that typically individuals are not comfortable discussing their gastrointestinal symptoms in an open forum with friends and colleagues [16]. In a survey of 5,576 patients, 75% of patients reported that their symptoms affected their ability to enjoy leisurely activities and 69% reported that their symptoms affected their ability to perform at work [15]. Importantly, though, over 70% of individuals who were on therapeutic agents reported improvements in their overall QOL [15]. Similarly, while the QOL with severe uncontrolled UC or immediately postsurgery was suboptimal, improvement in QOL was already noted 1 month after ileostomy take-down and returned to normal within one year after surgery for UC [17]. Potential predictors of reduced QOL include those with a higher perceived level of stress, less social support, greater number of disease relapses, and female sex [18].

When therapeutic modalities are successful in putting the disease in remission QOL is usually similar to the general population. However, when symptoms are not well controlled, especially in pediatrics, there can be a significant reduction in QOL [19]. Additionally, when therapeutic options result in side effects this further diminishes one's perception of QOL [20]. Importantly, the reduction in overall QOL in adolescence with IBD may be present regardless of disease activity. A study by MacKner et al. reported that patients with IBD had poorer school functioning compared to age matched controls [21].

Throughout this review the effects of women's issues in IBD and how they affect QOL will be addressed.

2.2. Menstruation

2.2.1. Puberty and Menarche. IBD may delay the onset of menses in adolescence, especially when the disease is poorly controlled [22, 23]. The exact etiology for this delay is unclear. Possible causes for this delay include growth failure from being underweight and nutritional deficits [22]. Medication usage, as the case with corticosteroids, also contributes to growth retardation and delayed puberty [24]. Additionally, in animal models, inflammatory mediators in active colitis may also contribute to malnourishment and pubertal delay. However, once disease is in a sustained remission, puberty and menarche occur soon after [25].

2.2.2. Symptoms and Changes during Menstrual Cycle. The hormonal changes during the menstrual cycle may affect a multitude of chronic disease symptoms and IBD is no exception [26]. In a study of 238 patients with IBD (151 CD, 87 UC) and 156 healthy controls, patients with CD were more likely to complain of an increase in diarrhea prior to and during menses, whereas patients with UC complained of an increase in diarrhea only during menses [27]. A recent study by Saha et al. found that changes in menses occurred even prior to the diagnosis of IBD [28]. In the year prior to the diagnosis of IBD, 21% of patients developed a change in the duration of menstrual flow [28]. Additionally, those suffering from dysmenorrhea had an increase in intensity of menstrual pain. This resulted in a significantly lower quality of life compared to those with more regular menstrual cycles. Over time, though, cycles became more regular [28].

If the physician and/or patients are not aware of these expected changes, many of them may be misinterpreted as exacerbations of the underlying IBD [29]. Therefore, counseling patients about expected fluctuations in symptoms that occur during the menstrual cycle is important in improving their overall quality of life.

2.3. Cervical Cancer Prevention and Screening

2.3.1. Risk of Cervical Cancer. Kane et al. reported that the overall incidence of any abnormal pap smear in a woman with IBD was 42.5% compared to 7% of controls [30]. Furthermore, women with IBD were more likely to be diagnosed with higher-grade lesions than controls [30]. Though not statistically significant, there was a trend toward those on immunosuppressants for greater than 6 months to have more abnormal pap smears [30]. The data on whether or not thiopurines increase the risk of cervical dysplasia is equivocal [31–33]. Recently, however, another population based study raises the possibility that IBD alone, regardless of thiopurine usage, may increase the risk of cervical neoplasia [34].

2.3.2. Screening for Cervical Cancer. Currently, the cervical cancer screening is recommended in the general female population every 2-3 years [35]. However, immunosuppressed patients, such as those with HIV, have recommendations to undergo yearly pap smears [36]. Given the equivocal evidence regarding the risk of cervical dysplasia from thiopurine usage,

some practices, like ours, recommend yearly pap smears. Nevertheless, yearly pap smears have not been advocated by major societies. Despite this concern for cervical dysplasia in this population, Singh et al. found that just over 50% of women with IBD underwent pap smears at guideline recommended intervals. Independent predictors of lower adherence to pap smears were CD and immunosuppressant usage [37].

2.3.3. Prevention of Cervical Cancer. Human papilloma virus (HPV) vaccinations, such as Cervarix and Gardasil, target HPV types 16 and 18, which are responsible for 70% of cervical cancers. Currently the Advisory Committee on Immunizations Practices (ACIP) recommends vaccinations for girls 9 years to 26 years of age [38]. Given the risk of abnormal pap smears, women on chronic immunosuppression are also candidates for HPV vaccination regardless of sexual activity status. Despite the beneficial effects of HPV vaccination, Wasan et al. found that the overall knowledge of gastroenterologists regarding appropriate vaccinations is poor [39].

2.4. Sexual Health

2.4.1. General Issues in Sexual Health. IBD can have a significant impact on a woman's sexual well-being [40]. Sexual activity may be a major component in considering what is "healthy." Sexuality, defined as the desire for sex and satisfaction with sexual activity, has been found to be lower in IBD patients [41]. There are multiple causes for this finding including the disease itself, medications, surgery, and its influence on energy level, libido, mood, and body image. Indirectly, there may be symptoms of fatigue and poor body image following surgery and use of medications like corticosteroids. Marín and colleagues found that 50% of women and 33% of men reported worsening sexual function after the diagnosis of IBD [42]. The disease itself may lead to issues with symptoms of diarrhea, fear of fecal incontinence, flatulence, and fistula drainage [43]. Impaired sexual activity is particularly worse in women with IBD compared to men with IBD; women with IBD were more likely to have impaired body image and decreased libido and engage in less intercourse [44]. In another study, women with IBD had lower sexual activity compared to age matched controls, but, interestingly, partner satisfaction was equally high [41]. The major factor affecting sexual activity, however, was related to concomitant depressed mood rather than disease activity [45]. As a result, in patients with reduced sexual satisfaction, it is important to both assess disease related issues and also screen for other potential causes like depression.

2.4.2. Sexual Issues after Surgery. Additional issues affecting sexual well-being are surgical treatments for IBD. Following surgical treatment for IBD, there is a significant concern of sexual dysfunction and dyspareunia [46]. Following a proctocolectomy in patients under 40, 33% of women complained of reduced quality of sexual life and 22% noted reduced satisfaction following intercourse after the surgery [47]. However, other studies have observed an improvement in sexual function. Metcalf et al. found that patients who undergo proctocolectomy with formation of either a Kock pouch or ileoanal anastomosis were more likely to increase their frequency of intercourse and had a reduction in the incidence of dyspareunia [48]. Damgaard et al. similarly reported finding increased sexual function and quality of life following ileal J-pouch anastomosis [49]. In a prospective study following ileal pouch-anal anastomosis, Davies et al. found that while abnormal sexual function decreased from 73% to 25% after surgery, the improvement in female sexual function took an average of 12 months postoperatively [50]. The type of surgical approach, whether laparoscopy versus conventional restorative proctocolectomy, did not lead to a difference in quality of life outcomes; however, laparoscopy is associated with improved cosmoses and body image which can affect one's sexual health [51]. In our center, our colorectal surgeons favor a laparoscopic approach whenever feasible.

Stoma formation carries many concerns with regard to its effect on sexual health. After formation of stoma, individuals have concerns about appliance leakage, odor, and body image [46]. Follick et al. surveyed patients with ostomies with 78% reporting a decrease in sexual activity; 34% had decreased enjoyment from sexual relations, and 41% felt sexual relations were a problem [52]. However, following ileostomy, patients noted unchanged or improved sexual function [53]. With adequate patient counseling regarding possible issues that can interfere with sexual relations and having adequate support services for the patient to address these issues if/when they come up, many of the concerns related to changes in sexual relations after surgery can be mitigated [54, 55]. As a result, we strongly recommend being proactive and initiating this discussion about sexual well-being with patients as a routine piece of the clinical assessment of women with IBD.

2.5. Fertility, Family Planning, and Contraception

2.5.1. Fertility. Women with IBD are often reluctant to discuss issues of family planning with their gastroenterologists. Fear of the unknown including likelihood of pregnancy, disease activity, its effects on an unborn child, and heritability of IBD in offspring may interplay with one another. This is particularly evident in a 2009 survey of patients with IBD who were queried on their views of subjective and objective views about fertility. While 42% of patients described some fear of infertility, the rate of those seeking medical infertility advice was no different compared to the healthy population. Specific concerns identified in this population included IBD heritability, medication teratogenicity, and risk of congenital abnormalities [56]. In light of these concerns, multiple studies have unsurprisingly shown that voluntary childlessness is more common in women with IBD compared to healthy controls. In a study by Marri et al., 18% of CD and 14% of UC patients chose voluntary childlessness compared to 6% in healthy controls. Contraception use in the IBD cohort was lower than controls prior to the diagnosis of IBD but higher than healthy controls afterwards [57]. Similarly, a recent survey found that nearly 80% of the women with IBD

who did not have children in the study had chosen not to have kids and did not have any fertility issues [58].

It is important to note though that fertility is in fact reduced in cases where patients undergo surgery and have an IPAA. A meta-analysis by Waljee et al. reported the risk of infertility was increased threefold [59]. The weighted average infertility rate was 48% after IPAA [59]. The exact cause of this reduction in fertility is unknown. It is speculated that either it is related to the surgical manipulation in the pelvic area or secondary to adhesions resulting in damage to the reproductive organs [60]. Therefore, while not an ideal surgery, some may consider either a temporary diverting ileostomy or temporary ileorectal anastomosis until after childbearing is completed to avoid this risk reduction. However, Pabby et al. found that women who had underwent IPAA were able to achieve live births following in vitro fertilization at rates comparable to women with UC without IPAA and women unaffected by IBD [61].

2.5.2. Family Planning. It is thus important for the clinician to broach the possibility of pregnancy and importance of family planning. Ideally, women should have quiescent disease when conception occurs, as this portends a favorable prognosis for both mother and baby. The presence of active disease may cause lower rates of fertility, but, as mentioned above, when disease is in remission, fertility is similar to those without IBD [62, 63]. The risk of passing IBD on to an offspring ranges from 1.6 to 5.2% with one parent having the disease and up to 36% when two parents have the disease [64, 65]. Only two of the medications, methotrexate and thalidomide, used to treat IBD are category X agents and should absolutely not be used [63]. The majority of medications used to treat IBD are otherwise either category B or category C [63]. If the disease is in remission, the effect of IBD on pregnancy is generally thought to be minimal. Some studies have indicated risks of preterm birth, low birth weight, and small gestational age. However, all of these are more significant when the disease is active [60, 63]. Given the importance of staying on medication to treat the IBD and risk of complications if the disease is/becomes active, we recommend that all women with IBD who plan on conceiving be seen by a high-risk obstetrician and followed up closely by their gastroenterologist. A discussion regarding the management during pregnancy is beyond the scope of this review [63].

2.5.3. Contraception. Specific considerations should be given when advising contraception use in women with IBD. While all forms of contraception are available to this population including barrier protection, oral contraception, and intrauterine devices, the optimal method of contraception should have a low failure rate and minimally interfere with IBD. Failure rates of barrier protection as well as case reports of IBD flares occurring after IUD insertion should be considered [66, 67]. Authors have also suggested that the risk of thrombosis in oral contraceptives (OCP) may theoretically exacerbate a known risk of thrombosis in IBD [68]. However, there have been no trials to date linking the use of OCPs and compounded thrombosis risk in IBD. In our center, we do not limit the use of OCP even in patients with inflammation. We recommend usage of whatever contraception is recommended as the ideal modality by the gynecologist.

The interaction between oral contraception and concomitant medical therapy for IBD should also be considered. Antibiotics are commonly used in IBD. It has long been advised by physicians that use of antibiotics in the setting of OCP decreases the efficacy of OCPs [69]. The American College of Gynecology importantly notes though that this has been based on anecdotal reports. According to their 2006 report, only rifampin has been shown to be associated with lower oral contraceptive steroid levels [70]. The only guidance for OCP use has been through small prospective trials, which note that OCP levels were seen to be stable [71–73]. Absorption of OCPs has not been shown to differ from healthy controls based on predominantly ileal or colonic disease [68], although some expert opinions still suggest that there may be potential for decreased efficacy in CD with small bowel resection and/or malabsorption [74–76]. If breakthrough bleeding occurs on long term antibiotic therapy, alternative contraceptive methods should be used.

There has been some concern that OCP use can increase the risk of developing IBD or cause an increase in flares. A meta-analysis in 2008 found that, after adjusting for smoking, exposure to OCPs increased the risk of IBD, in particular CD [77]. In a prospective cohort study examining the incidence of the development of IBD in the Nurse's Health Initiative, OCP use was associated with a small increase in the development of CD but not UC [78].

Because of evidence linking OCP use and risk of IBD, it has been postulated that OCPs may induce flares. In a literature review of the interaction between OCPs and IBD, Zapata et al. [68] found that the prevalence of relapse was not statistically significant in CD [79] or UC [80]. In a large prospective cohort of 331 women with CD, OCP use with progesterone only, low dose estrogen (30–35 mcg estrogen), and high dose estrogen (50 mcg estrogen) did not affect relapse rates [81]. More recently, in a 2014 article, Gawron et al. found that nearly 20% of women with IBD on OCPs reported improved GI symptoms related to menses while on OCPs [82]. As noted previously, there are case reports of IBD flares within IUD days to 24 months after placement, but larger studies and definite causality are lacking [66, 67].

2.6. Menopause

2.6.1. Menopause. Scant literature pertains to the effect of IBD on menopause and vice versa. However, women diagnosed with IBD may be diagnosed after the onset of menopause and the influence of hormonal changes on disease behavior is not clear.

A handful of articles give some insight into IBD and the timing of menopause. A study by Lichtarowicz et al. surveyed 196 women with CD from Wales about menstruation cycles, age of onset of menopause, smoking, and use of oral contraceptives. Forty-eight of these women underwent physiologic menopause with the mean age of menopause onset between

46 and 47 in the IBD group compared to 49.6 years in healthy controls [83]. In contrast, Kane and Reddy did not find any difference in median age of menopause in patients with IBD compared to healthy controls [84]. Additionally, there was no difference in occurrence of flares prior to or following the onset of menopause [84].

2.6.2. Hormone Replacement Therapy. Use of hormone replacement therapy (HRT) has been questioned since the Women's Health Initiative demonstrated an increase in risk of breast cancer, coronary artery disease, stroke, and venous thromboembolism [85]. HRT and its effect on IBD are unclear. Interestingly, Kane's study found a protective and dose dependent effect of HRT on disease activity in the postmenopausal state, with women with IBD on HRT 80% less likely to suffer from flares compared to those who were not on HRT [84].

More recently, use of HRT has been correlated with increased risk of development of UC. Khalili et al. prospectively followed up 108,844 women on HRT. The risk of development of UC was increased and further increased with duration of HRT use [86]. This correlation was not seen with development of CD. However, the correlation between HRT and flaring IBD remains unknown.

3. Conclusion

The health maintenance of patient with IBD has been increasingly emphasized. IBD affects women in many important ways. For the female patient diagnosed with IBD, gastroenterologists should be proactive with discussions about the course of the disease and its impact on menstruation, family planning, and menopause. In adolescence, careful proactive counseling regarding impact of IBD on QOL is critical. Physicians need to discuss with patients the effects both IBD and the medications used to treat IBD have on the onset of puberty and possible delays in onset of menarche. Additionally, women should be counseled about the potential increased risk in cervical cancer and means to reduce these risks with HPV vaccination and pap smears. The effect of IBD as well as the surgical treatments and the resultant impact on sexual relations is significant. While some of the issues may improve (e.g., ileostomy take-down), other issues like depression need to be sought out by the physician. Physicians should establish an open dialogue with patients early on regarding their sexual health and any issues related to it. While establishing this dialogue, careful attention to family planning is critical. Patients should be counseled about the use of OCPs and physicians should discuss how to optimize their disease status prior to attempting any pregnancy. Aside from patients with an IPAA, overall fertility should not be affected by IBD. Given potential complications associated with pregnancy we strongly encourage comanagement of these patients with a high-risk obstetrician. Overall, counseling the women with IBD about potential changes in puberty, menstruation, fertility, pregnancy, sexual health, and menopause is critical to optimizing their care. Such discussions allow the patient to develop realistic expectations and allay fears and concerns about the disease and its impact on important milestones that often go unaddressed. Given the knowledge deficit in the patient population, it is of utmost importance to not only present these topics, but guide women through any concerns and questions. Ultimately, future studies are still needed to improve the overall medical management and surgical management and to also clarify ways to improve the QOL in women with IBD.

Conflict of Interests

Authors have no relevant conflict of interests related to this paper.

References

[1] J. D. Feuerstein and A. S. Cheifetz, "Ulcerative colitis: epidemiology, diagnosis, and management," *Mayo Clinic Proceedings*, vol. 89, no. 11, pp. 1553–1563, 2014.

[2] A. S. Cheifetz, "Management of active Crohn disease," *The Journal of the American Medical Association*, vol. 309, no. 20, pp. 2150–2158, 2013.

[3] S. Wilks, "Morbid appearances in the intestine of Miss Bankes," *London Medical Times & Gazette*, vol. 2, p. 264, 1859.

[4] P. Nandivada, V. Poylin, and D. Nagle, "Advances in the surgical management of inflammatory bowel disease," *Current Opinion in Gastroenterology*, vol. 28, no. 1, pp. 47–51, 2012.

[5] J. Cosnes, C. Gowerrousseau, P. Seksik, and A. Cortot, "Epidemiology and natural history of inflammatory bowel diseases," *Gastroenterology*, vol. 140, no. 6, pp. 1785–1794, 2011.

[6] B. B. Crohn, L. Ginzburg, and G. D. Oppenheimer, "Regional ileitis: a pathological and clinical entity," *The Journal of the American Medical Association*, vol. 251, no. 1, pp. 73–79, 1932.

[7] P. Rutgeerts, K. Geboes, G. Vantrappen, J. Beyls, R. Kerremans, and M. Hiele, "Predictability of the postoperative course of Crohn's disease," *Gastroenterology*, vol. 99, no. 4, pp. 956–963, 1990.

[8] N. A. Molodecky, I. S. Soon, D. M. Rabi et al., "Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review," *Gastroenterology*, vol. 142, no. 1, pp. 46–54.e42, 2012.

[9] E. V. Loftus Jr., "Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences," *Gastroenterology*, vol. 126, no. 6, pp. 1504–1517, 2004.

[10] E. I. Benchimol, K. J. Fortinsky, P. Gozdyra, M. van den Heuvel, J. van Limbergen, and A. M. Griffiths, "Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends," *Inflammatory Bowel Diseases*, vol. 17, no. 1, pp. 423–439, 2011.

[11] N. A. Molodecky, I. S. Soon, D. M. Rabi et al., "Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review," *Gastroenterology*, vol. 142, no. 1, pp. 46.e42–54.e42, 2012.

[12] R. D. Johnston and R. F. A. Logan, "What is the peak age for onset of IBD?" *Inflammatory Bowel Diseases*, vol. 14, supplement 2, pp. S4–S5, 2008.

[13] G. Vernier-Massouille, M. Balde, J. Salleron et al., "Natural history of pediatric Crohn's disease: a population-based cohort study," *Gastroenterology*, vol. 135, no. 4, pp. 1106–1113, 2008.

[14] M. B. Heyman, B. S. Kirschner, B. D. Gold et al., "Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry," *Journal of Pediatrics*, vol. 146, no. 1, pp. 35–40, 2005.

[15] S. Ghosh and R. Mitchell, "Impact of inflammatory bowel disease on quality of life: results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey," *Journal of Crohn's and Colitis*, vol. 1, no. 1, pp. 10–20, 2007.

[16] H. R. Clearfield, "How does IBD affect quality of life?" *Inflammatory Bowel Diseases*, vol. 14, pp. S45–S46, 2008.

[17] A. J. Muir, L. J. Edwards, L. L. Sanders et al., "A prospective evaluation of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis," *The American Journal of Gastroenterology*, vol. 96, no. 5, pp. 1480–1485, 2001.

[18] A. Moradkhani, L. J. Beckman, and J. H. Tabibian, "Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors," *Journal of Crohn's and Colitis*, vol. 7, no. 6, pp. 467–473, 2013.

[19] M. de Boer, M. Grootenhuis, B. Derkx, and B. Last, "Health-related quality of life and psychosocial functioning of adolescents with inflammatory bowel disease," *Inflammatory Bowel Diseases*, vol. 11, no. 4, pp. 400–406, 2005.

[20] R. K. Cross, O. Lapshin, and J. Finkelstein, "Patient subjective assessment of drug side effects in inflammatory bowel disease," *Journal of Clinical Gastroenterology*, vol. 42, no. 3, pp. 244–251, 2008.

[21] L. M. MacKner, R. M. Bickmeier, and W. V. Crandall, "Academic achievement, attendance, and school-related quality of life in pediatric inflammatory bowel disease," *Journal of Developmental & Behavioral Pediatrics*, vol. 33, no. 2, pp. 106–111, 2012.

[22] A. B. Ballinger, M. O. Savage, and I. R. Sanderson, "Delayed puberty associated with inflammatory bowel disease," *Pediatric Research*, vol. 53, no. 2, pp. 205–210, 2003.

[23] A. Ferguson and D. M. Sedgwick, "Juvenile onset inflammatory bowel disease: height and body mass index in adult life," *British Medical Journal*, vol. 308, no. 6939, pp. 1259–1263, 1994.

[24] R. Heuschkel, C. Salvestrini, R. M. Beattie, H. Hildebrand, T. Walters, and A. Griffiths, "Guidelines for the management of growth failure in childhood inflammatory bowel disease," *Inflammatory Bowel Diseases*, vol. 14, no. 6, pp. 839–849, 2008.

[25] C. E. Brain and M. O. Savage, "Growth and puberty in chronic inflammatory bowel disease," *Baillière's Clinical Gastroenterology*, vol. 8, no. 1, pp. 83–100, 1994.

[26] J. Moore, D. Barlow, D. Jewell, and S. Kennedy, "Do gastrointestinal symptoms vary with the menstrual cycle?" *British Journal of Obstetrics and Gynaecology*, vol. 105, no. 12, pp. 1322–1325, 1998.

[27] M. T. Bernstein, L. A. Graff, L. E. Targownik et al., "Gastrointestinal symptoms before and during menses in women with IBD," *Alimentary Pharmacology and Therapeutics*, vol. 36, no. 2, pp. 135–144, 2012.

[28] S. Saha, Y.-Q. Zhao, S. A. Shah et al., "Menstrual cycle changes in women with inflammatory bowel disease: a study from the Ocean State Crohn's and Colitis Area Registry," *Inflammatory Bowel Diseases*, vol. 20, no. 3, pp. 534–540, 2014.

[29] S. M. Lim, C. M. Nam, Y. N. Kim et al., "The effect of the menstrual cycle on inflammatory bowel disease: a prospective study," *Gut and Liver*, vol. 7, no. 1, pp. 51–57, 2013.

[30] S. Kane, B. Khatibi, and D. Reddy, "Higher incidence of abnormal Pap smears in women with inflammatory bowel disease," *The American Journal of Gastroenterology*, vol. 103, no. 3, pp. 631–636, 2008.

[31] H. Singh, A. A. Demers, Z. Nugent, S. M. Mahmud, E. V. Kliewer, and C. N. Bernstein, "Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study," *Gastroenterology*, vol. 136, no. 2, pp. 451–458, 2009.

[32] M. A. Smith, P. M. Irving, A. M. Marinaki, and J. D. Sanderson, "Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease," *Alimentary Pharmacology & Therapeutics*, vol. 32, no. 2, pp. 119–130, 2010.

[33] C. W. Lees, J. Critchley, N. Chee et al., "Lack of association between cervical dysplasia and IBD: a large case-control study," *Inflammatory Bowel Diseases*, vol. 15, no. 11, pp. 1621–1629, 2009.

[34] C. Rungoe, J. Simonsen, L. Riis, M. Frisch, E. Langholz, and T. Jess, "Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study," *Clinical Gastroenterology and Hepatology*, vol. 13, no. 4, pp. 693–700.e1, 2015.

[35] V. A. Moyer, "Screening for cervical cancer: U.S. preventive services task force recommendation statement," *Annals of Internal Medicine*, vol. 156, no. 12, pp. 880–891, 2012.

[36] ACOG Committee on Practice Bulletins—Gynecology, "ACOG Practice Bulletin No. 117: Gynecologic care for women with human immunodeficiency virus," *Obstetrics & Gynecology*, vol. 116, no. 6, pp. 1492–1509, 2010.

[37] H. Singh, Z. Nugent, A. A. Demers, and C. N. Bernstein, "Screening for cervical and breast cancer among women with inflammatory bowel disease: a population-based study," *Inflammatory Bowel Diseases*, vol. 17, no. 8, pp. 1741–1750, 2011.

[38] L. E. Markowitz, E. F. Dunne, M. Saraiya et al., "Human papillomavirus vaccination: recommendations of the advisory committee on immunization practices (ACIP)," *Morbidity and Mortality Weekly Report*, vol. 63, pp. 1–30, 2014.

[39] S. K. Wasan, J. A. Coukos, and F. A. Farraye, "Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge," *Inflammatory Bowel Diseases*, vol. 17, no. 12, pp. 2536–2540, 2011.

[40] A. B. Trachter, A. I. Rogers, and S. R. Leiblum, "Inflammatory bowel disease in women: impact on relationship and sexual health," *Inflammatory Bowel Diseases*, vol. 8, no. 6, pp. 413–421, 2002.

[41] A. Timmer, D. Kemptner, A. Bauer, A. Takses, C. Ott, and A. Fürst, "Determinants of female sexual function in inflammatory bowel disease: a survey based cross-sectional analysis," *BMC Gastroenterology*, vol. 8, article 45, 2008.

[42] L. Marín, M. Mañosa, E. Garcia-Planella et al., "Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey," *Journal of Gastroenterology*, vol. 48, no. 6, pp. 713–720, 2013.

[43] G. A. Moody and J. F. Mayberry, "Perceived sexual dysfunction amongst patients with inflammatory bowel disease," *Digestion*, vol. 54, no. 4, pp. 256–260, 1993.

[44] K. R. Muller, R. Prosser, P. Bampton, R. Mountifield, and J. M. Andrews, "Female gender and surgery impair relationships, body image, and sexuality in inflammatory bowel disease: patient perceptions," *Inflammatory Bowel Diseases*, vol. 16, no. 4, pp. 657–663, 2010.

[45] A. Timmer, A. Bauer, A. Dignass, and G. Rogler, "Sexual function in persons with inflammatory bowel disease: a survey with matched controls," *Clinical Gastroenterology and Hepatology*, vol. 5, no. 1, pp. 87–94, 2007.

[46] B. Christensen, "Inflammatory bowel disease and sexual dysfunction," *Gastroenterology & Hepatology*, vol. 10, no. 1, pp. 53–55, 2014.

[47] M. Scaglia, G. G. Delaini, and L. Hultén, "Sexual dysfunctions after conventional proctocolectomy," *Chirurgia Italiana*, vol. 44, no. 5-6, pp. 230–242, 1992.

[48] A. M. Metcalf, R. R. Dozois, and K. A. Kelly, "Sexual function in women after proctocolectomy," *Annals of Surgery*, vol. 204, no. 6, pp. 624–627, 1986.

[49] B. Damgaard, A. Wettergren, and P. Kirkegaard, "Social and sexual function following ileal pouch-anal anastomosis," *Diseases of the Colon & Rectum*, vol. 38, no. 3, pp. 286–289, 1995.

[50] R. J. Davies, B. I. O'Connor, C. Victor, H. M. Macrae, Z. Cohen, and R. S. McLeod, "A prospective evaluation of sexual function and quality of life after ileal pouch-anal anastomosis," *Diseases of the Colon & Rectum*, vol. 51, no. 7, pp. 1032–1035, 2008.

[51] M. S. Dunker, W. A. Bemelman, J. F. M. Slors, P. van Duijvendijk, and D. J. Gouma, "Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study," *Diseases of the Colon & Rectum*, vol. 44, no. 12, pp. 1800–1807, 2001.

[52] M. J. Follick, T. W. Smith, and D. C. Turk, "Psychosocial adjustment following ostomy," *Health Psychology*, vol. 3, no. 6, pp. 505–517, 1984.

[53] P. Weerakoon, "Sexuality and the patient with a stoma," *Sexuality and Disability*, vol. 19, no. 2, pp. 121–129, 2001.

[54] M. R. Gloeckner, "Partner reaction following ostomy surgery," *Journal of Sex and Marital Therapy*, vol. 9, no. 3, pp. 182–190, 1983.

[55] J. N. Brouillette, E. Pryor, and T. A. Fox Jr., "Evaluation of sexual dysfunction in the female following rectal resection and intestinal stoma," *Diseases of the Colon and Rectum*, vol. 24, no. 2, pp. 96–102, 1981.

[56] R. Mountifield, P. Bampton, R. Prosser, K. Muller, and J. M. Andrews, "Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions," *Inflammatory Bowel Diseases*, vol. 15, no. 5, pp. 720–725, 2009.

[57] S. R. Marri, C. Ahn, and A. L. Buchman, "Voluntary childlessness is increased in women with inflammatory bowel disease," *Inflammatory Bowel Diseases*, vol. 13, no. 5, pp. 591–599, 2007.

[58] M. Mañosa, M. Navarro-Llavat, L. Marín, Y. Zabana, E. Cabré, and E. Domènech, "Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey," *Scandinavian Journal of Gastroenterology*, vol. 48, no. 4, pp. 427–432, 2013.

[59] A. Waljee, J. Waljee, A. M. Morris, and P. D. R. Higgins, "Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis," *Gut*, vol. 55, no. 11, pp. 1575–1580, 2006.

[60] U. Mahadevan, "Fertility and pregnancy in the patient with inflammatory bowel disease," *Gut*, vol. 55, no. 8, pp. 1198–1206, 2006.

[61] V. Pabby, S. S. Oza, L. E. Dodge et al., "In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis," *The American Journal of Gastroenterology*, 2014.

[62] M. Hudson, G. Flett, T. S. Sinclair, P. W. Brunt, A. Templeton, and N. A. G. Mowat, "Fertility and pregnancy in inflammatory bowel disease," *International Journal of Gynecology & Obstetrics*, vol. 58, no. 2, pp. 229–237, 1997.

[63] S. W. Ng and U. Mahadevan, "My treatment approach to management of the pregnant patient with inflammatory bowel disease," *Mayo Clinic Proceedings*, vol. 89, no. 3, pp. 355–360, 2014.

[64] R. A. Bennett, P. H. Rubin, and D. H. Present, "Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease," *Gastroenterology*, vol. 100, no. 6, pp. 1638–1643, 1991.

[65] H. Yang, C. McElree, M.-P. Roth, F. Shanahan, S. R. Targan, and J. I. Rotter, "Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews," *Gut*, vol. 34, no. 4, pp. 517–524, 1993.

[66] M. Cox, J. Tripp, and S. Blacksell, "Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network*: 5-year report," *Journal of Family Planning and Reproductive Health*, vol. 28, no. 2, pp. 73–77, 2002.

[67] J. G. Wakeman, "Exacerbation of Crohn's disease after insertion of a levonorgestrel intrauterine system: a case report," *Journal of Family Planning and Reproductive Health Care*, vol. 29, no. 3, p. 154, 2003.

[68] L. B. Zapata, M. E. Paulen, C. Cansino, P. A. Marchbanks, and K. M. Curtis, "Contraceptive use among women with inflammatory bowel disease: a systematic review," *Contraception*, vol. 82, no. 1, pp. 72–85, 2010.

[69] B. D. Dickinson, R. D. Altman, N. H. Nielsen, and M. L. Sterling, "Drug interactions between oral contraceptives and antibiotics," *Obstetrics and Gynecology*, vol. 98, no. 5, pp. 853–860, 2001.

[70] ACOG Committee on Practice Bulletins-Gynecology, "ACOG practice bulletin. No. 73: use of hormonal contraception in women with coexisting medical conditions," *Obstetrics & Gynecology*, vol. 107, pp. 1453–1472, 2006.

[71] A. Flynn and S. Kane, "Antibiotics and oral contraceptive efficacy in inflammatory bowel disease," *The American Journal of Gastroenterology*, vol. 106, no. 6, pp. 1174–1175, 2011.

[72] S. E. Helms, D. L. Bredle, J. Zajic, D. Jarjoura, R. T. Brodell, and I. Krishnarao, "Oral contraceptive failure rates and oral antibiotics," *Journal of the American Academy of Dermatology*, vol. 36, no. 5, pp. 705–710, 1997.

[73] F. Maggiolo, G. Puricelli, M. Dottorini, S. Caprioli, W. Bianchi, and F. Suter, "The effect of ciprofloxacin on oral contraceptive steroid treatments," *Drugs under Experimental and Clinical Research*, vol. 17, no. 9, pp. 451–454, 1991.

[74] S. F. Grimmer, D. J. Back, M. L. Orme, A. Cowie, I. Gilmore, and J. Tjia, "The bioavailability of ethinyloestradiol and levonorgestrel in patients with an ileostomy," *Contraception*, vol. 33, no. 1, pp. 51–59, 1986.

[75] J. P. Hanker, "Gastrointestinal disease and oral contraception," *American Journal of Obstetrics and Gynecology*, vol. 163, no. 6, pp. 2204–2207, 1990.

[76] L. Nilsson, A. Victor, J. Kral, E. Johansson, and N. Kock, "Absorption of an oral contraceptive gestagen in ulcerative colitis before and after proctocolectomy and construction of a continent ileostomy," *Contraception*, vol. 31, no. 2, pp. 195–204, 1985.

[77] J. Cornish, E. Tan, C. Simillis, S. Clark, J. Teare, and P. P. Tekkis, "The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis," *The American Journal of Gastroenterology*, vol. 103, no. 9, pp. 2394–2400, 2008.

[78] H. Khalili, L. M. Higuchi, A. N. Ananthakrishnan et al., "Oral contraceptives, reproductive factors and risk of inflammatory bowel disease," *Gut*, vol. 62, no. 8, pp. 1153–1159, 2013.

[79] J. P. Wright, "Factors influencing first relapse in patients with Crohn's disease," *Journal of Clinical Gastroenterology*, vol. 15, no. 1, pp. 12–16, 1992.

[80] A. Bitton, M. A. Peppercorn, D. A. Antonioli et al., "Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis," *Gastroenterology*, vol. 120, no. 1, pp. 13–20, 2001.

[81] J. Cosnes, F. Carbonnel, F. Carrat, L. Beaugerie, and J.-P. Gendre, "Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study," *Gut*, vol. 45, no. 2, pp. 218–222, 1999.

[82] L. M. Gawron, A. Goldberger, A. J. Gawron, C. Hammond, and L. Keefer, "The impact of hormonal contraception on disease-related cyclical symptoms in women with inflammatory bowel diseases," *Inflammatory Bowel Diseases*, vol. 20, no. 10, pp. 1729–1733, 2014.

[83] A. Lichtarowicz, C. Norman, B. Calcraft, J. S. Morris, J. Rhodes, and J. Mayberry, "A study of the menopause, smoking, and contraception in women with Crohn's disease," *Quarterly Journal of Medicine*, vol. 72, no. 267, pp. 623–631, 1989.

[84] S. V. Kane and D. Reddy, "Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease," *The American Journal of Gastroenterology*, vol. 103, no. 5, pp. 1193–1196, 2008.

[85] J. E. Rossouw, G. L. Anderson, R. L. Prentice et al., "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial," *The Journal of the American Medical Association*, vol. 288, pp. 321–333, 2002.

[86] H. Khalili, L. M. Higuchi, A. N. Ananthakrishnan et al., "Hormone therapy increases risk of ulcerative colitis but not Crohn's disease," *Gastroenterology*, vol. 143, no. 5, pp. 1199–1206, 2012.