



Sexual Dysfunction and Fertility Problems in Men with Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that is usually diagnosed in young individuals. Crohn's disease and ulcerative colitis are the 2 principal forms of IBD. Patients with IBD demonstrate varying degrees of disease activity and sometimes need to undergo bowel surgery such as proctocolectomy with ileal pouch-anal anastomosis that involves removal of the entire colon and rectum with consequent sexual dysfunction. Several studies have shown that sulfasalazine, affects male fertility. Additionally, many men with IBD are unable to control their smoking, drinking, and eating habits, which can cause worsening of disease activity and fertility. Therefore, infertility and sexual dysfunction are important issues in young patients diagnosed with IBD because they are related to optimal management of the disease and patients' quality of life. Only a few studies have reported sexual dysfunction and infertility in men with IBD. Therefore, this study reviewed the current literature describing male sexual dysfunction scales and evaluated the causes of sexual dysfunction and infertility in men with IBD.

Keywords: Crohn's disease; Erectile dysfunction; Inflammatory bowel diseases; Male infertility; Sexual dysfunction, physiological; Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that is usually diagnosed in young individuals between 15 and 40 years of age [1,2]. Crohn's disease (CD) and ulcerative colitis (UC) are the 2 principal forms of IBD. IBD is more common in Western countries than in other parts of the world; however, its prevalence is rapidly increasing in Asia, particularly in Korea [3,4]. Although IBD can occur at any age, based on current studies, the median ages at diagnosis of UC and CD in Koreans

are 35 years and 21.5 years, respectively [3]. Patients with IBD show an early onset of symptoms and undergo various medical treatments in their 20s, 30s, or 40s. Therefore, improving sexual dysfunction (SD) and quality of life in these patients is important. Additionally, the rate of SD in patients with IBD is 45% to 60% in women and 15% to 25% in men [5,6], which is higher than the SD rates of 30% and 5% in women and men, respectively, observed in the general population [7,8]. Therefore, SD is a serious concern among many patients with IBD and significantly affects patients' quality of life. Only a few studies have described SD

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in men with IBD. SD is associated with infertility and other pregnancy-related complications [9]. Patients with IBD demonstrating disease aggravation and requiring surgery and medical therapy, may develop infertility and lifestyle habits that could cause sexual difficulties [9,10]. This study reviewed SD in men with UC and CD.

INFLAMMATORY BOWEL DISEASE AND SEXUAL DYSFUNCTION

1. Assessment of sexual dysfunction in patients with inflammatory bowel disease

Several studies have reported the use of different questionnaires and/or indices to assess quality of life (including sexual function) in patients with IBD. The Inflammatory Bowel Disease Quality of Life Questionnaire [11] includes only 1 question regarding sexual function, which is, "To what extent has your bowel problem limited sexual activity during the last 2 weeks?" [11]. Notably, no definite IBD-specific validated questionnaires are available to evaluate SD in patients with IBD. Several studies have been performed using general validated questionnaires and the International Index of Erectile Function (IIEF) [12].

1) The International Index of Erectile Dysfunction

IIEF is the most commonly used scale to assess male SD. The IIEF comprises 15 questions categorized into 5 domains of sexual function as follows: i) erectile function (Q 1, 2, 3, 4, 5, 15 [6 items]), ii) orgasmic function (Q 9, 10 [2 items]), iii) sexual desire (Q 11, 12 [2 items]), iv) satisfaction with intercourse (Q 6, 7, 8 [3 items]), and v) overall satisfaction (Q 13, 14 [2 items]). Each question is assigned 0 to 5 points. Most questions (6/15) are associated with erectile function and are primarily applicable to the general elderly patient population [12]. Therefore, the IIEF is limited in assessing SD in most young patients with IBD. However, this tool is the most common questionnaire evaluating sexual function; thus, it has been applied to patients with IBD.

2) Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction measures

The Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction measure (PROMIS SexFS) (version 2.0) was developed and validated for the general population, including

patients with chronic diseases [13,14]. The SexFS items are not disease-specific, but include items that evaluate satisfaction with the disease and symptoms. This tool measures sexual function and satisfaction within 30 days prior to the administration of the survey and is applicable to both sexes. For men, 4 domains are included as follows: erectile function, interest in sexual activity, orgasmic ability, and satisfaction with sex life [13]. Higher the SexFS score, higher the interest in sexual activity and satisfaction with sex life.

3) European Organization for Research and Treatment of Cancer Study Group on Quality of Life

The European Organization for Research and Treatment of Cancer Study Group on Quality of Life (EORTC-QLQ) is a tool that assesses the quality of life in patients with colorectal cancer. It includes questions regarding sexual function and satisfaction, as well as colorectal issues such as fecal continence and stoma function [15]. Timmer et al [16] reported that feeling attractive ($p=0.002$) or feeling masculine ($p=0.005$) were significantly influenced by disease activity in patients with IBD (based on the EORTC questionnaire) ($p<0.05$).

4) Inflammatory bowel disease-male sexual dysfunction scale

O'Toole et al [17] reported a new IBD-specific psychometric tool to assess sexual function in men with IBD. They used a cross-sectional survey utilizing the IIEF to evaluate male sexual function, as well as the Patient Health Questionnaire to evaluate depressive symptoms and patients' medical history and sociodemographic information to identify clinical factors associated with SD [17]. They identified 10 items that were included in the IBD-specific-male SD scale. No endoscopic data support this study, and this being a recently published study, it is difficult to confirm its reliability. However, it may serve as a new tool to measure sexual function and psychometric factors in men with IBD. The various questionnaires and/or tools to assess male sexual function have been summarized in Table 1.

2. Definitions

1) Sexual dysfunction

SD is an important cause of male infertility and is categorized as erectile dysfunction (ED), decreased li-

Table 1. Comparison between questionnaires evaluating male sexual function

Questionnaire	IBD-specific	Sexual function-specific
IIEF	No	Yes
IBD-Q	Yes	No
The PROMIS Sexual Function and Satisfaction	No	Yes
EORTC-QLQ-CR 38	No	No
IBD-MSDS	Yes	Yes

IBD: inflammatory bowel disease, IIEF: International Index of Erectile Function, IBD-Q: inflammatory bowel disease quality of life questionnaire, PROMIS: Patient-Reported Outcomes Measurement Information System, EORTC-QLQ-CR 38: The 38-item European Organization for Research and Treatment of Cancer Study Group on Quality of Life questionnaire, IBD-MSDS: Inflammatory Bowel Disease-Male Sexual Dysfunction Scale.

bido, and abnormal ejaculation [2]. Additionally, physiological and psychological factors such as body image perception, fertility concerns, and sexual desire also affect sexual function [2,18].

2) Infertility

Infertility is defined as the inability to conceive within 12 months of unprotected sexual intercourse [19]. Primary infertility is defined as inability to conceive after 12 months despite regular unprotected sexual intercourse. Secondary infertility is defined as the inability to conceive after the birth of one or more biological children [20].

3. Causes of sexual dysfunction

1) Surgery

Surgery is recommended in patients with IBD who are refractory to conventional medical therapy or in patients who develop complications such as intestinal obstruction and toxic megacolon, which is defined as colonic diameter >6 cm leading to colonic perforation and/or massive hemorrhage [21,22]. Patients with CD commonly develop complications including perianal abscesses, fistulas, and stenosis, necessitating surgery [23]. The ostomy rate in patients with severe perianal CD is 31% to 49% [24,25]. Patients with CD undergo various operations including seton placement, stricturoplasty, fistulotomy, and colectomy with ostomy [23]. The risk of malignancy associated with the detection of high-grade dysplasia and dysplasia-associated lesions or masses also commonly necessitates elective operations

in patients with UC [21]. Previously, total proctocolectomy with end-ileostomy was the standard operation performed in patients with UC [26]; however, currently the most frequently performed procedure is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) [27]. IPAA preserves the anal transition zone; therefore, normal defecation is maintained. However, the most common complication of IPAA is pouchitis (a non-specific inflammation of the ileal pouch) [21,27]. Proctocolectomy can injure the parasympathetic and sympathetic nerves intraoperatively, and/or cause fibrosis, anatomical alterations, and psychological disturbances [28]. Previous studies have investigated the role of the aforementioned surgeries in causing SD in men with IBD. Farouk et al [29] reported a study involving 762 men with UC who underwent IPAA and observed that 3% of these men developed retrograde or no ejaculation 10 years after IPAA. Berndtsson et al [30] reported that 12% of men with UC developed SD (ejaculatory dysfunction) after IPAA. A meta-analysis of 43 observational studies that reported post-IPAA complications showed that 21 studies examined SD and 3.6% of the 5,112 patients investigated reported SD [31]. A few studies have shown that age is an important risk factor for SD. Lindsey et al. showed a 3.8% impotence rate in patients undergoing rectal dissection surgery, and all patients were aged >50 years [32]. Another study investigating the long-term outcomes after IPAA in young patients (median age at operation=18 years, and median follow-up=12.5 years) reported that no man showed impotence or retrograde ejaculation [33].

Several studies [32,34] have shown that IPAA improves overall sexual functional outcomes and satisfaction despite SD. Gorgun et al [34] showed that the mean erectile function score increased to 2.12 points postoperatively ($p=0.02$); however, no significant difference was observed in complete and partial ED pre- and postoperatively ($p=0.29$). Furthermore, a randomized, double-blind placebo-controlled trial investigating sildenafil (Viagra, a selective type-5 phosphodiesterase inhibitor), for ED in patients with IBD reported that 79% of men who underwent proctectomy showed improved erectile function [35].

In addition to IPAA, the other surgical options for IBD include end-ileostomy, ileo-rectal anastomosis, ileo-anal anastomosis without a pouch, and the Koch pouch [10]; however, data regarding postoperative SD associated with these options are limited. A survey-based

cross-sectional analysis performed in 280 men reported that creation of a stoma is associated with ED and diminished sexual satisfaction [16]. Kuruvilla et al [36] also reported that patients with UC who underwent ileostomy showed lower sexuality and body image scores than patients who underwent total proctocolectomy with IPAA. Therefore, although previous studies support the association between surgery and SD (Table 2), and although it is proven that sildenafil effectively manages postoperative SD, further research is needed to investigate in detail the effects of various types of surgeries on sexual function.

2) Medical therapy

(1) 5-aminosalicylic acid

Aminosalicylates are compounds containing 5-aminosalicylic acid (5-ASA) that show anti-inflammatory and immunomodulatory effects in the intestine. Sulfasalazine and mesalamine (which does not contain sulfa groups) are the commonly used agents in this category [37,38]. Sulfasalazine comprises 5-ASA and sulfapyridine. Sulfapyridine metabolites can adversely affect sperm and cause oligospermia, poor sperm motility, and increased risk of morphologically abnormal sperm [39,40]. However, several studies have reported reversal of adverse effects and restoration of function after discontinuation of 5-ASA [39,41-43]. In another

study, 555 patients with UC were administered long-term sulfasalazine and 5-ASA. Of these 555 patients, 42 men showed abnormal semen parameters as follows: impaired motility (90.5%), increased abnormal sperm morphology (47.6%), and reduced sperm concentration (38%). However, when 5-ASA was switched to another medication, all male fertility parameters improved after 3 months [44]. Riley et al [45] reported that among 9 of the 16 men with UC who switched to mesalamine (a 5-ASA compound without the sulfapyridine component), all 9 showed improved semen parameters. Several reports have described improvements in seminal fluid parameters in men who were switched to mesalamine [44,45]. However, a case report has described the development of oligospermia after mesalamine use in a young man [46]. Notably, discontinuation of the medication improved semen parameters to near-normal, and the patient's wife became pregnant thereafter [46]. Based on disease activity and a couple's desire to get pregnant, it is advisable to discontinue sulfasalazine or switch this medication to a different 5-ASA agent (without the sulfapyridine compound), if complete cessation of 5-ASA is contraindicated.

(2) Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that are commonly used in patients with acute or moderate-to-severe disease activity in patients with

Table 2. Studies summarizing operations and sexual dysfunction in patients with IBD

Type of operation	Studies evaluating sexual dysfunction & infertility
IPAA	<ul style="list-style-type: none"> • 3% of men with UC [29] <ul style="list-style-type: none"> - Retrograde or no ejaculation 10 years after IPAA • 12% of men with UC [30] <ul style="list-style-type: none"> - Ejaculatory dysfunction • Meta-analysis of 21 studies [31] <ul style="list-style-type: none"> - 3.6% of 5,112 patients evaluated - Sexual dysfunction such as retrograde ejaculation, erection disorder, and dyspareunia • Patients with IBD aged ≥50 years [32] <ul style="list-style-type: none"> - 3.8% impotence rate • Young patients (median age 18 years) who underwent IPAA surgery [33] <ul style="list-style-type: none"> - No impotence or retrograde ejaculation • 122 men who underwent IPAA surgery [34] <ul style="list-style-type: none"> - 2.12 point increase in the erectile function score (better sexual results) - No significant difference between pre- and postoperative erectile dysfunction (p=0.29)
Total proctocolectomy with end-ileostomy	<ul style="list-style-type: none"> • Patients with UC [36] <ul style="list-style-type: none"> - Lower sexuality and body image scores
Stoma	<ul style="list-style-type: none"> • 280 men with IBD [16] <ul style="list-style-type: none"> - Erectile dysfunction and decreased sexual satisfaction

UC: ulcerative colitis, IPAA: ileal pouch-anal anastomosis, IBD: inflammatory bowel disease.

IBD [47,48]. Corticosteroids inhibit several inflammatory pathways, such as the interleukin (IL) and the nuclear factor kappa-light-chain-enhancer of activated B cell complex pathways and also trigger apoptosis of gut lymphocytes [47]. There is a lack of research on the relationship between steroids and infertility. Lerman et al [49] investigated the effects of corticosteroids on reproduction in male rats and observed reversible adverse effects on accessory sex organs such as decreased weight and changes in the prostate and seminal vesicles of the animals without any changes in the sperm count, motility, or morphology. Burnell et al [50] compared family size in patients with CD who were administered steroids or sulfasalazine. They showed that family size decreased independent of medical therapy, and no significant difference was observed between men who did not receive steroids and those who received steroids for <6 and >6 months. Additionally, the administration of steroids concomitant with the immunomodulator azathioprine (AZA), did not adversely affect semen quality [51]. Therefore, no significant association was observed between corticosteroid use and male infertility. However, large-scale studies are needed to draw definitive conclusions in this regard.

(3) Immunomodulators

Immunomodulators are drugs that modify the activity of the immune system and also possess anti-inflammatory properties. Patients may show symptom resolution several months after using the medication. However, maintenance and combination therapy are used in patients with IBD [47]. AZA and 6-mercaptopurine (6-MP) are the main immunomodulators used in patients with IBD, in addition to methotrexate (MTX), cyclosporine, and tacrolimus [47,51].

① Thiopurines

Thiopurines such as AZA and 6-MP are useful to maintain remission in steroid-dependent or refractory cases of IBD for their steroid-sparing effect [52,53]. AZA is a prodrug and non-enzymatically metabolized to 6-MP; however, 6-MP is metabolized by thiopurine S-methyl transferase to 6-thioguanine nucleotides and 6-methylmercaptapurine (Fig. 1) [54,55].

A few studies using animal models have shown AZA-induced teratogenicity causing malformations of the extremities and genetic injury to sperm [55,56]. In another study [57], the incidence of pregnancy-related complications was higher in women who became pregnant within 3 months of using 6-MP than in women in whom the drug was discontinued or not used at all [57]. However, several other studies report a negative association between thiopurine and infertility in patients with IBD [51,58,59]. Dejaco et al [51] reported the influence of AZA therapy on semen quality in men with IBD as follows: 18 men showed no difference in sperm density, motility, morphology, ejaculate volume, or the total sperm count evaluated by semen analyses before and after AZA treatment. However, when concomitant therapy with sulfasalazine was used, semen quality was diminished. Francella et al [58] reported a retrospective cohort study comprising 155 patients with IBD (79 women and 76 men) and showed that 6-MP did not produce adverse pregnancy outcomes, such as major congenital abnormalities, spontaneous abortions, anembryonic pregnancy, and embryonic demise. Teruel et al [59] showed no significant difference in unsuccessful pregnancies among couples in whom the men received mercaptopurine and AZA when compared with the control group. A meta-analysis showed that thiopurine use in women with IBD was associated with preterm birth, despite no association with low birth weight and/

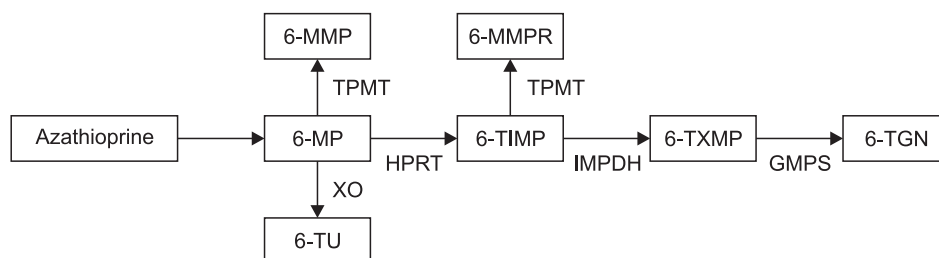


Fig. 1. Figure showing thiopurine metabolism. 6-MMP: 6-methylmercaptapurine, 6-MP: 6-mercaptopurine, 6-TU: 6-thiouric acid, TPMT: thiopurine S-methyltransferase, XO: xanthine oxidase, HPRT: hypoxanthine phosphoribosyltransferase, 6-MMPR: 6-methylmercaptapurine riboside, 6-TIMP: 6-thioinosine 5'-monophosphate, IMPDH: inosine 5'-monophosphate dehydrogenase, 6-TXMP: 6-thioxanthylic acid, GMPS: guanosine 5'-monophosphate synthetase, 6-TGN: 6-thioguanine nucleotides.

or congenital abnormalities. In men with IBD, thiopurine use was not associated with the risk of congenital abnormalities (pooled odds ratio, 1.87; 95% confidence interval, 0.67–5.25) [60]. Adverse pregnancy outcomes have been reported in animal studies and in a few human studies; however, overall it does not appear to significantly affect male sexual function. However, men with IBD whose partners are planning to become pregnant need to be fully aware of the potential adverse effects of this therapy to choose the optimal medication.

② Methotrexate

MTX is a dihydrofolate reductase inhibitor, and its cytotoxic effect is unclear [47]. It is known to inhibit cytokine and eicosanoid synthesis and effectively treats several autoimmune diseases including IBD secondary to its anti-inflammatory action [47]. MTX is often used as a second-line immunomodulatory agent in patients with IBD who are resistant or intolerant to AZA or 6-MP [47]. It is contraindicated during pregnancy owing to its teratogenicity [61]. There is a lack of studies discussing the association between MTX and male SD; however, MTX is associated with oligospermia owing to its anti-folate actions with consequent inhibition of DNA synthesis and cell proliferation [38]. MTX potentially affects sexual functions through its cytotoxic, teratogenic, and mutagenic actions [62-64]. Cytotoxicity plays a role at the level of spermatogenesis or *via* direct injury to the sperm after crossing the blood–testis barrier causing oligospermia or dysfunctional sperm. Teratogenicity of MTX might be caused by transfer of chemicals to the female partner *via* seminal fluid during sexual intercourse. Mutagenicity of MTX is related to its role in altering genetic material that is at risk of inheriting the affected sperm [62,65]. In animal studies, MTX has been shown to cause significant disruption of the basement membrane, as well as produce cytotoxic effects on seminiferous tubule proliferation, and degeneration of spermatocytes and Sertoli and Leydig cells [66]. Grunnet et al [67] reported that the adverse effects of MTX manifested by abnormal semen analysis performed in 10 men with severe psoriasis using MTX were not significantly different from those in men using steroids. El-Beheiry et al [68] reported no significant abnormalities in terms of semen quality, testicular histopathological features, and spermatogenic activity in 26 men with psoriasis receiving MTX. Recently, Ley et al [69] published a case-control study that investigated

the effects of MTX on sperm quality and genetic integrity. Notably, 7 men with IBD who received MTX for >3 months showed significantly decreased sperm integrity and DNA fragmentation and damage secondary to oxidative stress compared with age-matched men in a study performed across different fertility centers.

However, although MTX therapy affects sperm integrity, to date, the pregnancy-related adverse effects of MTX-exposed male's offspring are unclear [10]. Sussman and Leonard [70] reported severe oligospermia in men receiving MTX for severe psoriasis; however, normal sperm concentrations were observed after discontinuation of MTX. Therefore, the authors recommended that men whose partners are planning to conceive should discontinue MTX therapy 36 months prior to planning the pregnancy [61].

③ Cyclosporine and tacrolimus

Cyclosporine A (CsA) and tacrolimus are classified as category C medications for use during pregnancy by the Food and Drug Administration [61]. CsA is a calcineurin inhibitor, which causes immunosuppression of T cells through blockage of *IL-2* gene transcription [47]. In animal models, CsA use in male rats has been shown to cause abnormal sperm, oligospermia, abnormal sperm motility, decreased testis weight and serum testosterone concentration [38,71]. In another study, high-dose (10 mg/kg/d) CsA usage was associated with decreased sperm motility and serum testosterone levels [38,72]. However, the dose used in the study was relatively high compared with doses commonly used in patients with IBD. A meta-analysis of 15 studies reported that CsA did not cause significant adverse events, such as prematurity, major malformations, and low birth weight [73]. A few case studies have reported the safety of CsA use at 27 weeks in women with fulminant UC. No study has discussed infertility in men with IBD using CsA.

Tacrolimus is also a calcineurin inhibitor that is often used in steroid-refractory thiopurine naïve patients with UC [74]. Tacrolimus use is associated with a 5.6% rate of malformations [61] and a high incidence of perinatal hyperkalemia and prematurity [75,76]. A case study of pregnancy and neonatal outcomes associated with tacrolimus use in patients showing refractory UC reported successful pregnancy outcomes and childbirth [77].

(4) Anti-tumor necrosis factor agents

Tumor necrosis factor- α (TNF- α) is a pro-inflammatory cytokine with a significant role in chronic inflammatory diseases such as IBD, rheumatoid arthritis, and psoriasis [78]. Anti-TNF agents such as infliximab (IFX) and adalimumab (ADA) are important treatment options for patients with moderate-to-severe active IBD as induction and maintenance therapy [38,47]. IFX is a chimeric monoclonal immunoglobulin (Ig) G1 antibody against TNF, and ADA is a human anti-TNF monoclonal antibody that is administered as a subcutaneous injection [78]. A few studies have investigated the effects of IFX in men with IBD. A few other studies have investigated the association between anti-TNF agents and male fertility. In one study of 146 patients who were exposed to IFX before and after pregnancy, 131 women were exposed directly and 15 women were indirectly exposed through partners, of which only 10 of 15 exposed by men were available outcome data. And they did not show adverse outcomes [79]. Mahadevan et al [72] reported that IFX therapy in 10 men with IBD showed a significant increase in semen volume until a week after infusion; however, men who received IFX as maintenance therapy showed a lower rate of normal oval forms of sperm after infusion. Moreover, the study suggested a possible mechanism to explain the TNF-re-

lated changes in sperm motility and morphology. Spermiogenesis occurs in the testicular syncytium. The process of transformation of spermatids into spermatozoa involves "individualization" of sperm to remove nearly the entire cytoplasm. This process of cytoplasmic extrusion is mediated by Drosophila by TNF- α dependent caspase family proteases [80]. Anti-TNF- α can block TNF activity and reduce the caspase activity with consequent extrusion of the cytoplasm from the sperm during the natural process of development. This may be related to abnormal sperm motility and morphology [72]. Puchner et al [81] reported a systematic review of 60 cases in which expectant fathers used anti-TNF agents before their partners conceived and this did not cause adverse pregnancy outcomes and male infertility. Data regarding the association between anti-TNF and male infertility are limited, and further research is needed.

(5) Other biological agents

Recently, various biological agents such as anti-integrin agents (natalizumab, vedolizumab) and anti-IL 12-23 (ustekinumab) have been used in patients with IBD in addition to the use of anti-TNF agents. Anti-TNF agents that are not as commonly used as IFX and ADA (certolizumab and golimumab) are also being ad-

Table 3. Association between medical therapy and pregnancy-related factors in men with inflammatory bowel disease

	Sexual dysfunction & infertility	Adverse events of pregnancy	Recommendation
Sulfasalazine	<ul style="list-style-type: none"> • Erectile dysfunction • Oligospermia • Poor sperm motility • Increased forms of abnormal sperm (reversible) [41-45] 	Possible (congenital malformations) [10]	Stop medication or switch to a different class of 5-ASA medications
Mesalamine	Oligospermia [46]	No	Discontinue only in patients with stable disease
Corticosteroids	No	No	Recommended short-term use
Thiopurines	No	Controversial [51,58,59]	Counsel regarding the possibility of teratogenic effects on sperm
MTX	<ul style="list-style-type: none"> Erectile dysfunction Altered spermatogenesis Oligospermia Teratogenicity [62-65] 	No [10]	Discontinue in patients with erectile dysfunction
Cyclosporine	Decreased sperm motility and testosterone (high dose) [38,72]	No [73]	No recommendations
Infliximab	Decreased sperm motility and abnormal sperm morphology [72]	No [79]	No recommendations
Other biological agents	No [83]	No [10,81-84]	No recommendations

5-ASA: 5-aminosalicylic acid, MTX: methotrexate.

ministered to patients with IBD [81]. Notably, few studies have discussed the association between newer biological agents and male reproductive function. Based on a few previous studies, the use of biological agents in pregnant women with IBD is associated with a low risk [81]. Natalizumab is a human IgG4 monoclonal antibody with immunomodulatory action *via* its role in blocking the $\alpha 4$ subunits of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin molecules of the immune system [82]. Ebrahimi et al [82] reported pregnancy and fetal outcomes in 101 women with multiple sclerosis who received natalizumab and showed no adverse pregnancy outcomes. Vedolizumab is a gut-specific IgG1 monoclonal antibody to $\alpha 4\beta 7$ integrin [83]. Mahadevan et al [83] assessed pregnancy outcomes in total 46 women, including 27 women who received vedolizumab and 19 women who were exposed by male partners. Of the 19 women (whose partners received vedolizumab), 11 had normal births, 2 were spontaneous abortions, 3 were elective terminations, and 3 had undocumented outcomes in the study. Although this study included a small sample size, there were no significant differences in pregnancy outcomes between healthy patients in the control group and vedolizumab users [83]. Ustekinumab is an IgG1 monoclonal antibody and acts as an inhibitor of IL-12 and IL-23 receptors [84]. Cortes et al [85] reported a case report of a woman with CD who received ustekinumab who conceived during treatment and delivered a healthy infant even with maintenance ustekinumab therapy. We summarized the association between medical therapy and pregnancy-related factors in men with IBD (Table 3).

3) Disease activity

Disease activity is an important parameter because the extent of disease activity of IBD determines the treatment regimen. Patients present with symptoms such as abdominal pain, diarrhea, and bleeding during the active disease phase of IBD [47]. A few studies have suggested that disease activity could affect the results of semen analysis and male sexual function [5,10]. Reportedly, the stage of active inflammation in patients with IBD tends to be associated with the release and action of inflammation-related pro-inflammatory cytokines such as TNF- α and IL-1, and oxidative stress, which may affect fertility [86]. Bel et al [5] showed that men with active IBD demonstrated a greater degree of SD than men undergoing remission or healthy con-

trols. These men showed a lower rate of orgasms and overall sexual satisfaction than healthy controls and a higher rate of SD (greater ED and lower orgasmic ability, desire and sexual gratification) than men with IBD undergoing remission. Timmer et al [87] reported that men with IBD showing remission or mild disease did not show any difference in SD compared with healthy controls; however, men with IBD with severe active disease show a greater degree of SD such as erectile and orgasmic dysfunction and lower sexual desire and satisfaction than healthy controls. Therefore, controlling IBD is important in men whose partners are planning to conceive or actually conceive.

4) Nutrition and lifestyle factors including smoking and alcohol intake

Based on the European Society for Parenteral and Enteral Nutrition guidelines, it is known that malnutrition is highly prevalent in patients with IBD [88], and poor nutritional status in men with IBD might cause SD [89]. Zinc is an important factor involved in male fertility. Zinc plays an important role in optimal testicular function by affecting sperm motility, spermatogenesis, and maintaining optimal serum androgen levels [90]. El-Tawil [90] suggested that zinc deficiency may contribute to male infertility. Abbasi et al [91] reported oligospermia in 4 of 5 men with a restricted zinc intake over 24 to 40 weeks.

Alcohol and tobacco are known to cause well-known effects in patients with IBD. Alcohol use in patients with IBD is known to cause relapse or symptom aggravation from an inactive state [92]. Several studies have shown an association between alcohol consumption and fertility, including the effects of alcohol on testicular atrophy, decreased libido, and a decrease in the sperm count [93,94].

Smoking is a known risk factor for CD, although it shows a protective effect in patients with UC [1]. The exact mechanism that explains this difference is unclear. Several studies have reported an association between smoking and sexual function in men and reported that smoking causes a reduction in the sperm count and density, and also affects sperm motility and morphology [94,95]. No studies have discussed the effects of smoking in patients with IBD. However, the deleterious effects of alcohol and tobacco are well-documented and the use of these substances should be discontinued. Therefore, the direct relevance of lifestyle including

nutrition, alcohol and tobacco to infertility and SD in IBD patients is unclear and further research is needed.

5) Psychological factors

Quality of life and sexual functions are affected by symptoms such as diarrhea, fatigue, and abdominal pain in men with IBD. Additionally, depression is commonly reported to be associated with decreased quality of life [47,96]. Gollenberg et al [97] reported an association between stressful life events and semen parameters in that stressful life events led to diminished semen quality. The most common hypothesis in this regard is that stressful events may cause lowering of serum levels of testosterone and luteinizing hormone, which consequently interferes with spermatogenesis [98,99]. Timmer et al [87] reported a study in which 153 men with IBD were compared with matched pairs and showed similar sexual function; however, depression led to SD, which manifested as ED, low sexual desire, and low levels of overall satisfaction. Additionally, Bel et al [5] suggested that depression is the most important factor associated with SD in patients with IBD. Therefore, optimal management of the quality of life and psychological factors is important in patients with IBD. Further studies are required to investigate these and related issues.

CONCLUSIONS

Epidemiological data show that IBD predominantly affects relatively young patients of reproductive age. Therefore, adequate knowledge of the several factors causing IBD-induced SD is important. This study reviewed the association between male sexual function and surgery, medication, lifestyle habits such as alcohol and tobacco use, nutritional status, and psychological factors in men with IBD. Although no large-scale studies have been performed in this context, most studies suggest that 5-ASA and MTX should be discontinued before conception, if possible. The role of rectal surgery and medications including AZA, steroids, and biological agents is controversial, although no study has reported significant adverse effects on pregnancy outcomes associated with their use. Therefore, treatment needs to be individualized through discussion with physicians considering the disease activity and specific clinical situations. Additionally, this review revealed that discontinuing alcohol and tobacco use, improving nutritional

status, and improving mental health help to control the disease and improve patients' quality of life.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: YEP. Data curation: YEP. Formal analysis: YEP. Investigation: YEP. Methodology: YEP. Validation: TOK. Visualization: YEP. Writing—original draft: YEP. Writing—review & editing: TOK.

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