World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4292/wjgpt.v7.i3.361

World J Gastrointest Pharmacol Ther 2016 August 6; 7(3): 361-369
ISSN 2150-5349 (online)

TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Infertility in men with inflammatory bowel disease

Takeshi Shin, Hiroshi Okada

Takeshi Shin, Hiroshi Okada, Department of Urology, Dokkyo Medical University Koshigaya Hospital, Saitama 343-8555, Japan

Author contributions: Shin T designed the study, performed the literature review, and wrote the manuscript; Okada H collected data and analyzed them and performed critical revision of the manuscript for important intellectual content; all authors gave final approval of the version of the manuscript to be published.

Conflict-of-interest statement: The authors declare no conflict of interest related to this publication.

Manuscript source: Invited manuscript

Correspondence to: Takeshi Shin, MD, Assistant Professor, Department of Urology, Dokkyo Medical University Koshigaya Hospital, 2-1-50 Minamikoshigaya, Koshigaya City, Saitama 343-8555, Japan. shintakeshi@nifty.com
Telephone: +81-48-9651111
Fax: +81-46-9651111

Received: April 5, 2016
Peer-review started: April 5, 2016
First decision: June 6, 2016
Revised: June 19, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: August 6, 2016

Abstract

Inflammatory bowel disease (IBD) predominantly affects young adults. Fertility-related issues are therefore important in the management of patients with IBD. However, relatively modest attention has been paid to reproductive issues faced by men with IBD. To investigate the effects of IBD and its treatment on male fertility, we reviewed the current literature using a systematic search for published studies. A PubMed search were performed using the main search terms "IBD AND male infertility", "Crohn's disease AND male infertility", "ulcerative colitis AND male infertility". References in review articles were used if relevant. We noted that active inflammation, poor nutrition, alcohol use, smoking, medications, and surgery may cause infertility in men with IBD. In surgery such as proctocolectomy with ileal pouch-anal anastomosis, rectal incision seems to be associated with sexual dysfunction. Of the medications used for IBD, sulfasalazine reversibly reduces male fertility. No other medications appear to affect male fertility significantly, although small studies suggested some adverse effects. There are limited data on the effects of drugs for IBD on male fertility and pregnancy outcomes; however, patients should be informed of the possible effects of paternal drug exposure. This review provides information on fertility-related issues in men with IBD and discusses treatment options.

Key words: Crohn's disease; Infertility; Inflammatory bowel disease; Male; Ulcerative colitis

Core tip: In men with inflammatory bowel disease (IBD), factors such as surgery, medications, disease activity, and poor nutritional status are thought to contribute to infertility. Surgery with rectal incision is associated with sexual dysfunction (*e.g.*, erectile dysfunction, anejaculation, and retrograde ejaculation). Among medications, sulfasalazine causes reversible qualitative and quantitative semen abnormalities. No other medications seem to affect male fertility significantly. There are limited data on the effects of paternal exposure to IBD medications on pregnancy outcomes, but no significant increase in fetal risk has been noted except for thiopurines. Patients should be

appropriately informed of possible effects of paternal drug exposure.

Shin T, Okada H. Infertility in men with inflammatory bowel disease. *World J Gastrointest Pharmacol Ther* 2016; 7(3): 361-369 Available from: URL: http://www.wjgnet.com/2150-5349/full/v7/i3/361.htm DOI: http://dx.doi.org/10.4292/wjgpt.v7.i3.361

INTRODUCTION

Inflammatory bowel disease (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) is a chronic intestinal disorder usually diagnosed in early adulthood. The incidence of IBD has been found to be the highest between the second and fourth decade of life[1], and fertility-related issues are therefore important clinical considerations.

Infertility is defined as a disease of the reproductive system characterized by failure to achieve a clinical pregnancy after ⩾ 12 mo of regular unprotected sexual intercourse[2]. Much attention has been focused on issues related to fertility in women with IBD, but relatively little attention has been paid to the reproductive issues faced by men with IBD. Male infertility is thought to be more prevalent in IBD patients than in the general population[3]. From a case control study, Moody *et al*[4] showed that the number of children born to men with CD is significantly lower in comparison to men with UC and the general population, but found no difference in the number of children between men with UC and the general population. Notably, the fecundability of the three groups did not differ significantly[5], and the frequency of sexual intercourse was not significantly different between the patients with IBD and the matched controls[6]. Heetun *et al*[7] suggested that the smaller family size might be due to a fear of passing on the disease to offspring or a decision to limit family size rather than a physical effect of the disease. A recent systematic review of non-surgically treated men with CD revealed a 18%-50% reduction in fertility with no difference in reproductive capacity[8].

Even if overall IBD itself does not seem to affect fertility in men, medications used to treat the disease, surgery, and malnutrition resulting from IBD may cause male infertility, including sexual dysfunction. Table 1 shows the possible causes of infertility in men with IBD. This article summarizes sexual and reproductive issues associated with male IBD patients.

Table 1 Possible causes of infertility in men with inflammatory bowel disease

Causes of infertility in men with IBD	Ref.
Surgery	[17,19-25]
Medications	[4,5,7,15,16,28-32,42,43]
Active disease	[15,16,76]
Poor nutrition	[15,77]
Alcohol use	[15,81-83]
Tobacco use	[15,83,86,87]
Psychological factor	[7,88,89]

IBD: Inflammatory bowel disease.

SURGERY CAUSING MALE INFERTILITY

It is estimated that approximately 25%-35% of UC patients will ultimately require surgery for either a complication of the disease or inadequate control of symptoms, and 70%-90% of CD patients will need a surgical intervention at some point in the course of their disease[9-11]. Surgery is required in cases of failure of medical management, risk of malignancy, intestinal obstruction and toxic megacolon. Especially in patients with CD, complications such as perianal abscesses, fistulas, and stenosis can occur during the course of the disease, and surgery is often indicated in these cases[12,13]. Surgical treatment of perianal fistulas ranges from minimal surgery like seton and fistulotomy to definitive surgery with closure of the fistula tract or proctectomy and fecal diversion[13]. Currently, the most frequently performed surgical procedure for UC is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA), while intestinal resection is the most commonly performed surgical procedure for CD[14].

Proctocolectomy with IPAA seems to be associated with sexual dysfunction in men[15,16]. The sexual disturbances after proctocolectomy are usually due to damage to parasympathetic and sympathetic nerves during surgery, but sometimes due to anatomical alterations, fibrosis, or psychological factors[17].

Sexual dysfunction is one of the etiologies of male infertility, and it includes erectile dysfunction and ejaculatory dysfunction such as retrograde ejaculation and anejaculation (no ejaculation). A meta-analysis found that the pooled incidence of sexual dysfunction from 21 studies comprising 5112 patients was 3.6%[18], but this meta-analysis included both men and women. When focusing on only men, Berndtsson *et al*[19] found that 12% of male patients with UC had ejaculatory dysfunction after IPAA. In a retrospective study, Hueting *et al*[20] showed the incidence of erectile dysfunction or retrograde ejaculation in such patients to be 25.7%. A study of 122 men who underwent IPAA found that the prevalence of retrograde ejaculation increased from 1.6% preoperatively to 8.2% postoperatively, but the prevalence of erectile dysfunction was similar before and after IPAA[21]. On the other hand, a large study by Farouk *et al*[22] found sexual dysfunction in 1% of male patients (n = 762) at 1 year after IPAA, and in 2% (n = 215) at 12 years after IPAA. Table 2 shows an overview of past studies of sexual function after proctocolectomy in men[17,19-25]. Regarding the treatment of sexual dysfunction due to rectal excision, there has been one randomized placebo-controlled trial for sildenafil for erectile dysfunction[26]. This study showed a successful

Table 2 Studies of sexual function after proctocolectomy in men

Ref.	Year	No. of patients	Disease	Time since surgery	Sexual dysfunction after surgery	
					ED	EjD
Michelassi *et al*[23]	1993	24	UC	1.5 yr (median)	0%	19%
Damgaard *et al*[24]	1995	26	UC	2.8 yr (median)	3.80%	3.80%
Farouk *et al*[22]	2000	762	UC	1 yr	1%	
		215	UC	12 yr	2%	
Slors *et al*[17]	2000	40	Benign disease	2.8 yr (median)	10%	12.50%
Lindsey *et al*[25]	2001	156	CD, UC	6.2 yr (median)	14%	0%
Berndtsson *et al*[19]	2004	25	UC	1 yr	0%	12%
Hueting *et al*[20]	2004	35	CD, UC	3.5 yr (median)	25.70%	
Gorgun *et al*[21]	2005	122	CD, UC, others	3.6 yr (median)	12%	8.20%

CD: Crohn's disease; ED: Erectile dysfunction; EjD: Ejaculatory dysfunction; UC: Ulcerative colitis.

response in 79% of patients in the sildenafil-treated group. Given these data, Feagins *et al*[15] suggested that they could reassure male patients that the occurrence of postoperative sexual dysfunction after IPAA for IBD is low and, when it does occur, it can be successfully treated with sildenafil in most cases. However, sperm banking should be offered before surgery considering that some patients with erectile dysfunction after IPAA fail to respond to medications and some patients may develop ejaculatory dysfunction after surgery, although they are few in number.

There are other surgical options for IBD apart from IPAA, but the data on postoperative fertility (or sexual function) remain limited. One report by Hultén suggested that ileo-rectal anastomosis has the advantage of avoiding rectal dissection and the associated risks of sexual disturbance, but increases the risk of cancer in the rectal stump[27]. Good results in colectomy with ileo-rectal anastomosis require appropriate patient selection, good rectal distensibility criteria, and accurate endoscopic and histological surveillance for prompt treatment of any recurrence of pouchitis or onset of premalignant changes[27].

MEDICATIONS CAUSING MALE INFERTILITY

Table 3 summarizes the effect of IBD medications on male fertility and the partner's pregnancy outcomes. It also notes recommendations for discontinuation of medications before attempting to conceive.

Sulfasalazine and 5-aminosalicylates

Sulfasalazine and 5-aminosalicylates (5-ASAs) have been used for the initial treatment of IBD and for long-term maintenance of disease remission[28]. These drugs have anti-inflammatory activity.

Levi *et al*[29] first reported 4 cases of male infertility associated with sulfasalazine in 1979. In all 4 cases, discontinuation of sulfasalazine led to successful conception. Subsequent studies showed that this medication causes reversible non-dose-dependent quantitative and qualitative abnormalities of sperm in > 80% of men[28,30,31]. Birnie *et al*[32] examined 21 men with CD who received sulfasalazine and found that 18 of them had abnormal semen analysis results and 15 had oligozoospermia. Another study by Moody *et al*[4] showed that 25% of men with IBD had no children, compared with 15% of men in the general population. They also found that 60% of male IBD patients who had no children were taking sulfasalazine. Sulfasalazine is a molecule that has two components: 5-ASA and sulfapyridine. The sulfapyridine metabolite is thought to be responsible for adverse effects on sperm, causing impaired sperm maturation or oxidative stress production[33-36]. However, Wu *et al*[37] found no correlation between reactive oxygen species production and sperm density, sperm motility, or hamster oocyte penetration capacity. The adverse effects of sulfasalazine on sperm have been shown to be fully reversible after discontinuation[29,31,33,36,38]. Restoration of semen quality and fertility has also been shown after switching to a different 5-ASA compound without the sulfapyridine component, such as mesalazine (also called mesalamine)[39,40]. Zelissen *et al*[41] evaluated semen quality in 11 patients with IBD during sulfasalazine treatment and 4 mo after replacing sulfasalazine with an oral slow-release preparation of 5-ASA, and observed significant improvements in sperm count, morphology, and motility during 5-ASA treatment in comparison with sulfasalazine treatment. Notably, 3 pregnancies occurred during the study period.

On the other hand, there is a case report of mesalazine-induced oligozoospermia in a young man with UC. In that case, semen analysis results returned to near normal and pregnancy occurred after mesalazine treatment was stopped, but the patient's semen parameters worsened after resuming mesalazine[42]. Moreover, we have reported a retrospective study of the negative influence of mesalazine on fertility in men with IBD[43]. In this study, 7 of 1225 male subfertile patients had received mesalazine. In 6 of them, mesalazine was discontinued and sperm motility and total motile sperm count were significantly improved. After discontinuation of mesalazine, 4 of the 6 patients achieved pregnancy with their partners.

Table 3 Effects of medications used for inflammatory bowel disease on male fertility

	Infertility	Pregnancy complications	Recommendations
Sulfasalazine	Reversible	One study	Switch to a different 5-ASA
Mesalazine	One study	None reported	Discontinue only in stable disease
Corticosteroids	No	None reported	Only use short periods
Thiopurines	No	Controversial	No recommendation
Methotrexate	Unclear	None reported	Discontinue in the case of erectile dysfunction
Ciclosporine	No	None reported	No recommendation
Infliximab	Unclear	None reported	No recommendation

5-ASA: 5-Aminosalicylate.

However, mesalazine should be discontinued in only patients with stable disease, and it is possible that low IBD activity itself might have contributed to the improved semen analysis results in the patients who discontinued mesalazine.

With respect to pregnancy complications, Moody *et al*[4] suggested an increased risk of congenital malformations in children born to men on sulfasalazine, but a meta-analysis examining the risk of adverse pregnancy outcomes in women with IBD after exposure to 5-ASAs including sulfasalazine showed no significant increase in congenital abnormalities, stillbirths, spontaneous abortions, preterm deliveries, or low birth weight[44].

From the evidence accumulated to date, discontinuation of sulfasalazine is recommended for prospective fathers, but not discontinuation of 5-ASA compounds lacking the sulfapyridine moiety.

Corticosteroids

Corticosteroids are potent anti-inflammatory agents used for moderate to severe relapses of both CD and UC, but they have no role in maintenance therapy. Corticosteroids inhibit several inflammatory pathways by suppression of interleukin transcription; induction of I-kappa B, which stabilizes the nuclear factor kappa B complex; suppression of arachidonic acid metabolism; and stimulation of apoptosis of lymphocytes within the lamina propria of the gut[45].

Limited data are available on the effects of corticosteroids therapy on fertility for men with IBD. Lerman *et al*[46] found a reversible reduction in fertility in rats exposed to corticosteroids in spite of no changes in sperm count and motility. In a study of 5 endurance-trained men, Roberts *et al*[47] showed that an increase in endogenous steroids might be correlated with a subsequent decrease in sperm concentration 74 d later. In contrast, in a study of 70 men with CD and a group of age-matched controls, Burnell *et al*[48] found no correlation between male infertility and steroid use. In a study of IBD patients undergoing azathioprine (AZA) treatment, the additional administration of corticosteroids had no negative influence on seminogram findings[49]. Definite conclusions regarding the effects of corticosteroids on male fertility cannot be drawn at present because of insufficient data.

Thiopurines

AZA and its active metabolite 6-mercaptopurine (6-MP) are widely used as adjunctive therapy in IBD and as corticosteroid-sparing therapies although they are unapproved therapies for IBD[47].

In a study of 18 men with IBD who received AZA, no worsening of semen analysis results was found, and 6 of the men fathered children during the study period[49]. In a survey of 164 male renal transplant recipients, Xu *et al*[50] concluded that long-term treatment with cyclosporine, AZA, and corticosteroid had no obvious effect on fertility.

A study of male mice exposed to 6-MP showed no reduction in sperm quantity or quality, but a significantly increased incidence of abortion was noted. The authors suggested that this indicated occult sperm damage[51]. In a study of male patients with IBD who were treated with 6-MP, Rajapakse *et al*[52] revealed that the incidence of pregnancy-related complications was significantly increased when the father had used 6-MP within 3 mo of conception. Another study showed that paternal use of AZA or 6-MP before conception was associated with an increased, but not statistically significant, risk of congenital abnormalities[16,53]. Conversely, Francella *et al*[54] found no significant difference in pregnancy outcomes for both men and women taking 6-MP as compared with controls. Teruel *et al*[55] evaluated the outcomes of pregnancies in which the father was exposed to thiopurines at the time of conception, and found no significant difference in unsuccessful pregnancies, namely, spontaneous abortions, ectopic pregnancies, anembryonic pregnancies, or fetal deaths. They concluded that routine alteration of treatment regimens was not recommended for men taking thiopurines when attempting to conceive. According to a review by Akbari *et al*[56] concerning the effects of thiopurines on birth outcomes, thiopurine exposure in men with IBD at the time of conception was not associated with congenital abnormalities[28].

In summary, thiopurines do not appear to deteriorate semen quality. Some studies have suggested that paternal thiopurine treatment is associated with an increased risk of pregnancy complications, but in most past studies, paternal thiopurine exposure was not related to congenital

abnormalities. Regarding the use of thiopurines in male IBD patients who wish to conceive, Sands *et al*[28] proposed that health care providers should inform them that there is a possibility of an increased risk of congenital defects and pregnancy complications although fertility does not seem to be affected.

Methotrexate

Methotrexate (MTX) is positioned as a second-line immunosuppressive agent used in patients resistant or intolerant to AZA or 6-MP. Polyglutamated metabolites of MTX act through the inhibition of dihydrofolate reductase, and the inhibition of cytokine and eicosanoid synthesis are thought to play a role[45].

MTX is known to have teratogenic effects in women, and it is classified by the American Foods and Drug Administration under Pregnancy Category X, which means that it is contraindicated during pregnancy[7]. However, data are scarce on the effect of MTX on male fertility. Studies of animals exposed to MTX showed altered spermatogenesis, cytotoxicity, and degeneration of spermatocytes, Sertoli cells, and Leydig cells[15,28,57,58]. In 1980, Sussman *et al*[59] reported severe oligozoospermia after MTX administration but a return to normal sperm concentrations after discontinuation of MTX. The antifolate mechanism of MTX, which results in decreased DNA synthesis rates and subsequent inhibition of cellular proliferation, likely causes reversible oligozoospermia[28]. El-Beheiry *et al*[60] investigated the effects of MTX on fertility potential in 26 male psoriatic patients. They showed no abnormalities in semen analysis, testicular histology, or spermatogenic function observed using radioactive phosphorus, although a longer follow-up was required to rule out the possible teratogenic effects of the drug.

There have been no reports of MTX-induced adverse pregnancy outcomes in men exposed to the drug. Recently, Weber-Schoendorfer *et al*[61] performed a prospective observational cohort study involving 113 pregnancies where the father was treated with low-dose MTX around the time of conception. As compared with 412 pregnancies without MTX exposure, no increase was observed in the rate of major birth defects or the risk of spontaneous abortion. Further, gestational age at delivery and birth weights did not differ significantly between the groups. Given these results, they concluded that it seems reasonable not to postpone family planning in the case of unavoidable paternal MTX therapy.

However, the active metabolites of MTX could remain in cells or tissues for several months after discontinuation[16]. Furthermore, MTX seems to be associated with erectile dysfunction[62-64]. In most of the literature reviews, discontinuation of MTX was recommended at least 3-4 mo before a planned conception for men with IBD[7,15,16].

Ciclosporin (cyclosporine)/tacrolimus

Ciclosporin (CsA) is a calcineurin inhibitor used for treating severe IBD. It prevents clonal expansion of T cell subsets with a rapid onset of action. Tacrolimus is another calcineurin inhibitor, and is often preferred in transplant recipients[45]. CsA and tacrolimus differ in their chemical structure: Tacrolimus is a macrocyclic lactone, while CsA is a cyclic endecapeptide. However, they act in a similar manner as calcineurin inhibitors.

In a review, Sands *et al*[28] introduced one study using male mice exposed to CsA, and remarked on the presence of abnormal sperm, oligozoospermia, decreased motility, decreased testicular weight, and decreased testosterone concentrations. A study in rats found that CsA had a deleterious effect on spermiogenesis by directly impairing spermiogenic cell development and by impeding Sertoli cell function[65]. In humans, small studies have not found an association between CsA use and male fertility[16,66-68]. There have been no reports of adverse pregnancy outcomes in partners of men receiving CsA.

Monoclonal antibodies against tumor necrosis factor-alpha

Three biological agents are used for the treatment of IBD, namely, infliximab (IFX), adalimumab, and certolizumab. All agents are monoclonal antibodies against tumor necrosis factor-alpha (anti-TNF). IFX is a chimeric anti-TNF antibody, consisting of 75% human IgG and 25% murine component. Adalimumab and certolizumab are humanized anti-TNF antibodies. These agents are indicated in CD resistant to standard immunosuppression therapy. IFX is also indicated in UC and fistulating CD[45].

Few studies have examined the effects of anti-TNF on male fertility. IFX is the most studied of the three agents[28]. One animal study using analogous anti-TNF agents revealed no adverse effect on male fertility[7,69]. In a study of 10 men (8 with IBD, 2 with indeterminate colitis), Mahadevan *et al*[70] showed a significant increase in semen volume one week after IFX infusion and a trend toward decreased sperm motility. In contrast, in a study of 26 men with spondyloarthritis, Villiger *et al*[71] showed no statistically significant difference in sperm quality between healthy controls and patients treated with anti-TNF. They recommended the continuation of anti-TNF treatment when fatherhood was planned. Further, in a prospective study of 10 men with spondyloarthritis and 20 healthy male controls, Ramonda *et al*[72] found a statistically significant decrease in sperm aneuploidies and normal hormone levels after a 12-mo anti-TNF regimen and concluded that anti-TNF agents appeared to be safe for testicular function and male fertility.

Exposure to anti-TNF agents in men prior to a planned conception does not seem to cause embryo toxicity. One study that investigated medical records of men with ankylosing spondylitis reported that 4 patients had fathered 6 healthy children during IFX treatment[73]. A systematic review by Puchner *et al*[74] did not found any documentation of miscarriages or physical abnormities associated with anti-TNF treatment and paternity. Instead, an improvement in sperm motility and vitality during anti-TNF treatment was shown in that review. The

authors suggested that the improvement might be due to a decrease in disease activity.

OTHER FACTORS CAUSING MALE INFERTILITY

Disease activity

Active disease seems to affect male reproductive and sexual function[15,16]. The presence of pro-inflammatory cytokines, including TNF, in the male urogenital tract could lead to cytokine-mediated antifertility effects. Furthermore, inflammation is associated with elevated levels of reactive oxygen species and oxidative stress, both of which have a negative effect on male fertility[75]. Regarding sexual function, Timmer *et al*[76] showed that men with IBD in remission or with mild disease activity had similar rates of erectile dysfunction as compared with controls, whereas men with severe IBD activity had higher rates. Thus, control of IBD activity is recommended for men planning to conceive.

Nutrition

Poor nutritional status in men with IBD might cause infertility. El-Tawil suggested a possible relation between decreased testicular function and zinc deficiency, which has been found in up to 70% of patients with CD[77]. To date, no other studies have specifically addressed the contribution of nutritional status to male infertility in IBD, but Feagins *et al*[15] proposed that optimizing nutritional status is important for men with IBD who are attempting to father children.

Alcohol use

There are several studies that implicate a negative effect of alcohol consumption on the course of IBD[78]. Swanson *et al*[79] showed that alcohol resulted in exacerbation of gastrointestinal symptoms in patients with non-active UC and CD. Jowett *et al*[80] indicated that alcohol consumption increased the risk of disease exacerbation in patients with UC. Thus, alcohol use could activate the disease in the patients with IBD. Moreover, past studies implicated alcohol use in decreasing sperm quality and fertility in men[15,81-83]. Alcohol is considered as one of factors that might be contributing to male infertility in men with IBD.

Tobacco use

Smoking is the most researched environmental factor associated with IBD. It has been observed that smoking has a varying impact on CD and UC, contributing to an increased risk for individuals with CD and a protective role in individuals with UC[1]. The mechanism of these paradoxical effects of smoking on CD and UC is not well understood. It is hypothesized that nicotine and oxidative stress play some role[1,84].

Even if smoking protects against UC, smoking itself impairs fertilization capacity[83]. Tobacco combustion produces many chemical compounds with potential deleterious effects on male germ cells[85]. The toxins originating from cigarette smoke can decrease sperm mitochondrial activity and damage the chromatin structure in human sperm[83]. From a recent meta-analysis of 20 studies with 5865 participants, smoking was found to be a significant risk factor for decreased semen parameters in men[86]. Therefore, smoking cessation is expected to have a positive influence on semen quality and consequently male fertility.

Psychological factor

Past studies showed lower birth rates to men after IBD diagnosis than before diagnosis compared with controls[5,48]. These results meant that IBD men might consider voluntary childlessness apart from physiological factors that could reduce fertility[87]. This voluntary childlessness appears to result from concerns about adverse reproductive outcomes that may not be justified, or patients' fear of transmitting the disease[7,88]. In a questionnaire survey, Mountifield *et al*[88] concluded that patients require accurate counseling addressing fertility and pregnancy outcomes in IBD to assist in their decision making.

TREATMENT OF INFERTILITY IN MEN WITH IBD

Active inflammation, lifestyle factors (alcohol use, tobacco use), medications, poor nutritional status, and rectal incision seem to affect fertility in male IBD patients[15]. First of all, it is important to control IBD activity. If the patient shows poor nutritional status, optimizing their nutritional status is recommended. Tobacco cessation is strongly recommended when the patient is a smoker. If possible, discontinuation of medications associated with male infertility is recommended for prospective fathers. Table 3 shows the recommendations for each drug. In patients taking sulfasalazine, switching to a different 5-ASA is advised at least 4 mo prior to attempting to conceive[28]. In patients with stable IBD who are receiving mesalazine, discontinuation of the drug might restore fertility[43]. To avoid any potential adverse events, corticosteroids should be used for short periods to control active disease[28]. Although discontinuation of MTX is recommended 3-4 mo before attempting to conceive in most of the past reviews, there is insufficient evidence for males to support this recommendation. The risks of MTX discontinuation might outweigh the unsubstantiated hypothetical benefits. Discontinuation should be considered only in the case of erectile dysfunction. At present, there is insufficient evidence to recommend discontinuation of thiopurines, CsA, and anti-TNF agents such as IFX. Sperm banking should be offered to patients who plan to undergo proctocolectomy, because postoperative anejaculation, despite its low incidence, is a potential irreversible complication.

CONCLUSION

This review aimed to provide further insights into relationship between IBD and male fertility, a topic that has received relatively little attention in the literature. Rectal incision can potentially lead to sexual dysfunction after surgery, and sexual dysfunction may cause male infertility. Of the medications used for IBD, sulfasalazine causes reversible oligoasthenoteratozoospermia. No other medications seem to significantly affect fertility in men although small studies suggested some adverse effects. In the case of erectile dysfunction, discontinuation of MTX should be considered because MTX appears to be associated with erectile dysfunction. There are limited data about the effects of other drugs on male fertility and pregnancy outcomes; however, patients should be appropriately informed of the possible effects of paternal drug exposure. Considering that IBD predominantly affects young adults of reproductive age, gastroenterologists treating IBD patients should pay more attention to fertility-related issues. Sperm banking is an option for fertility preservation before surgery or initiation of a potentially gonadotoxic medication.

REFERENCES

1 **Ponder A**, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. *Clin Epidemiol* 2013; **5**: 237-247 [PMID: 23922506 DOI: 10.2147/CLEP.S33961]

2 **Zegers-Hochschild F**, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril* 2009; **92**: 1520-1524 [PMID: 19828144 DOI: 10.1016/j.fertnstert.2009.09.009]

3 **Rossato M**, Foresta C. Antisperm antibodies in inflammatory bowel disease. *Arch Intern Med* 2004; **164**: 2283 [PMID: 15534172]

4 **Moody GA**, Probert C, Jayanthi V, Mayberry JF. The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire. *Int J Colorectal Dis* 1997; **12**: 220-224 [PMID: 9272451]

5 **Narendranathan M**, Sandler RS, Suchindran CM, Savitz DA. Male infertility in inflammatory bowel disease. *J Clin Gastroenterol* 1989; **11**: 403-406 [PMID: 2760429]

6 **Moody GA**, Mayberry JF. Perceived sexual dysfunction amongst patients with inflammatory bowel disease. *Digestion* 1993; **54**: 256-260 [PMID: 8243839]

7 **Heetun ZS**, Byrnes C, Neary P, O'Morain C. Review article: Reproduction in the patient with inflammatory bowel disease. *Aliment Pharmacol Ther* 2007; **26**: 513-533 [PMID: 17661756]

8 **Tavernier N**, Fumery M, Peyrin-Biroulet L, Colombel JF, Gower-Rousseau C. Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 847-853 [PMID: 24004045 DOI: 10.1111/apt.12478]

9 **Wexner SD**, Rosen L, Lowry A, Roberts PL, Burnstein M, Hicks T, Kerner B, Oliver GC, Robertson HD, Robertson WG, Ross TM, Senatore PJ, Simmang C, Smith C, Vernava AM, Wong WD. Practice parameters for the treatment of mucosal ulcerative colitis--supporting documentation. The Standards Practice Task Force. The American Society of Colon and Rectal Surgeons. *Dis Colon Rectum* 1997; **40**: 1277-1285 [PMID: 9369100]

10 **Berg DF**, Bahadursingh AM, Kaminski DL, Longo WE. Acute surgical emergencies in inflammatory bowel disease. *Am J Surg* 2002; **184**: 45-51 [PMID: 12135718]

11 **Gardiner KR**, Dasari BV. Operative management of small bowel Crohn's disease. *Surg Clin North Am* 2007; **87**: 587-610 [PMID: 17560414]

12 **Klag T**, Goetz M, Stange EF, Wehkamp J. Medical Therapy of Perianal Crohn's Disease. *Viszeralmedizin* 2015; **31**: 265-272 [PMID: 26557835 DOI: 10.1159/000434664]

13 **Seifarth C**, Kreis ME, Gröne J. Indications and Specific Surgical Techniques in Crohn's Disease. *Viszeralmedizin* 2015; **31**: 273-279 [PMID: 26557836 DOI: 10.1159/000438955]

14 **Hwang JM**, Varma MG. Surgery for inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 2678-2690 [PMID: 18461653]

15 **Feagins LA**, Kane SV. Sexual and reproductive issues for men with inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 768-773 [PMID: 19223893 DOI: 10.1038/ajg.2008.90]

16 **Palomba S**, Sereni G, Falbo A, Beltrami M, Lombardini S, Boni MC, Fornaciari G, Sassatelli R, La Sala GB. Inflammatory bowel diseases and human reproduction: a comprehensive evidence-based review. *World J Gastroenterol* 2014; **20**: 7123-7136 [PMID: 24966584 DOI: 10.3748/wjg.v20.i23.7123]

17 **Slors FJ**, van Zuijlen PP, van Dijk GJ. Sexual and bladder dysfunction after total mesorectal excision for benign diseases. *Scand J Gastroenterol Suppl* 2000; **(232)**: 48-51 [PMID: 11232492]

18 **Hueting WE**, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. *Dig Surg* 2005; **22**: 69-79 [PMID: 15838175]

19 **Berndtsson I**, Oresland T, Hultén L. Sexuality in patients with ulcerative colitis before and after restorative proctocolectomy: a prospective study. *Scand J Gastroenterol* 2004; **39**: 374-379 [PMID: 15125470]

20 **Hueting WE**, Gooszen HG, van Laarhoven CJ. Sexual function and continence after ileo pouch anal anastomosis: a comparison between a meta-analysis and a questionnaire survey. *Int J Colorectal Dis* 2004; **19**: 215-218 [PMID: 14564464]

21 **Gorgun E**, Remzi FH, Montague DK, Connor JT, O'Brien K, Loparo B, Fazio VW. Male sexual function improves after ileal pouch anal anastomosis. *Colorectal Dis* 2005; **7**: 545-550 [PMID: 16232233]

22 **Farouk R**, Pemberton JH, Wolff BG, Dozois RR, Browning S, Larson D. Functional outcomes after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Ann Surg* 2000; **231**: 919-926 [PMID: 10816636]

23 **Michelassi F**, Stella M, Block GE. Prospective assessment of functional results after ileal J pouch-anal restorative proctocolectomy. *Arch Surg* 1993; **128**: 889-894; discussion 894-895 [PMID: 8343061]

24 **Damgaard B**, Wettergren A, Kirkegaard P. Social and sexual function following ileal pouch-anal anastomosis. *Dis Colon Rectum* 1995; **38**: 286-289 [PMID: 7882794]

25 **Lindsey I**, George BD, Kettlewell MG, Mortensen NJ. Impotence after mesorectal and close rectal dissection for inflammatory bowel disease. *Dis Colon Rectum* 2001; **44**: 831-835 [PMID: 11391143]

26 **Lindsey I**, George B, Kettlewell M, Mortensen N. Randomized, double-blind, placebo-controlled trial of sildenafil (Viagra) for erectile dysfunction after rectal excision for cancer and inflammatory bowel disease. *Dis Colon Rectum* 2002; **45**: 727-732 [PMID: 12072621]

27 **Hultén L**. Proctocolectomy and ileostomy to pouch surgery for ulcerative colitis. *World J Surg* 1998; **22**: 335-341 [PMID: 9523513]

28 **Sands K**, Jansen R, Zaslau S, Greenwald D. Review article: the safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. *Aliment Pharmacol Ther* 2015; **41**: 821-834 [PMID: 25752753 DOI: 10.1111/apt.13142]

29 **Levi AJ**, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. *Lancet* 1979; **2**: 276-278 [PMID: 88609]

30 **Taffet SL**, Das KM. Sulfasalazine. Adverse effects and desensitization. *Dig Dis Sci* 1983; **28**: 833-842 [PMID: 6136396]

31 **O'Moráin C**, Smethurst P, Doré CJ, Levi AJ. Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984; **25**: 1078-1084 [PMID: 6148293]

32 **Birnie GG**, McLeod TI, Watkinson G. Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22**: 452-455 [PMID: 6114898]

33 **Toovey S**, Hudson E, Hendry WF, Levi AJ. Sulphasalazine and

male infertility: reversibility and possible mechanism. *Gut* 1981; **22**: 445-451 [PMID: 6114897]
34 **Fukushima T**, Hamada Y, Komiyama M, Matsuno Y, Mori C, Horii I. Early changes in sperm motility, acrosome reaction, and gene expression of reproductive organs in rats treated with sulfasalazine. *Reprod Toxicol* 2007; **23**: 153-157 [PMID: 17166698 DOI: 10.1016/j.reprotox.2006.10.003]
35 **Alonso V**, Linares V, Bellés M, Albina ML, Sirvent JJ, Domingo JL, Sánchez DJ. Sulfasalazine induced oxidative stress: a possible mechanism of male infertility. *Reprod Toxicol* 2009; **27**: 35-40 [PMID: 19028562 DOI: 10.1016/j.reprotox.2008.10.007]
36 **Linares V**, Alonso V, Domingo JL. Oxidative stress as a mechanism underlying sulfasalazine-induced toxicity. *Expert Opin Drug Saf* 2011; **10**: 253-263 [PMID: 21219240 DOI: 10.1517/14740338.2011.529898]
37 **Wu FC**, Aitken RJ, Ferguson A. Inflammatory bowel disease and male infertility: effects of sulfasalazine and 5-aminosalicylic acid on sperm-fertilizing capacity and reactive oxygen species generation. *Fertil Steril* 1989; **52**: 842-845 [PMID: 2572460]
38 **Cosentino MJ**, Chey WY, Takihara H, Cockett AT. The effects of sulfasalazine on human male fertility potential and seminal prostaglandins. *J Urol* 1984; **132**: 682-686 [PMID: 6147421]
39 **Riley SA**, Lecarpentier J, Mani V, Goodman MJ, Mandal BK, Turnberg LA. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28**: 1008-1012 [PMID: 2889648 DOI: 10.1136/]
40 **Chatzinoff M**, Guarino JM, Corson SL, Batzer FR, Friedman LS. Sulfasalazine-induced abnormal sperm penetration assay reversed on changing to 5-aminosalicylic acid enemas. *Dig Dis Sci* 1988; **33**: 108-110 [PMID: 2892654 DOI: 10.1007/BF01536639]
41 **Zelissen PM**, van Hattum J, Poen H, Scholten P, Gerritse R, te Velde ER. Influence of salazosulphapyridine and 5-aminosalicylic acid on seminal qualities and male sex hormones. *Scand J Gastroenterol* 1988; **23**: 1100-1104 [PMID: 2907823]
42 **Chermesh I**, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36**: 551-552 [PMID: 15334777]
43 **Shin T**, Kobori Y, Suzuki K, Iwahata T, Yagi H, Soh S, Arai G, Okada H. Inflammatory bowel disease in subfertile men and the effect of mesalazine on fertility. *Syst Biol Reprod Med* 2014; **60**: 373-376 [PMID: 25144125 DOI: 10.3109/19396368.2014.952391]
44 **Rahimi R**, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008; **25**: 271-275 [PMID: 18242053 DOI: 10.1016/j.reprotox.2007.11.010]
45 **Mowat C**, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60**: 571-607 [PMID: 21464096 DOI: 10.1136/gut.2010.224154]
46 **Lerman SA**, Miller GK, Bohlman K, Albaladejo V, Léonard JF, Devas V, Clark RL. Effects of corticosterone on reproduction in male Sprague-Dawley rats. *Reprod Toxicol* 1997; **11**: 799-805 [PMID: 9407590]
47 **Roberts AC**, McClure RD, Weiner RI, Brooks GA. Overtraining affects male reproductive status. *Fertil Steril* 1993; **60**: 686-692 [PMID: 8405526]
48 **Burnell D**, Mayberry J, Calcraft BJ, Morris JS, Rhodes J. Male fertility in Crohn's disease. *Postgrad Med J* 1986; **62**: 269-272 [PMID: 2872665]
49 **Dejaco C**, Mittermaier C, Reinisch W, Gasche C, Waldhoer T, Strohmer H, Moser G. Azathioprine treatment and male fertility in inflammatory bowel disease. *Gastroenterology* 2001; **121**: 1048-1053 [PMID: 11677195]
50 **Xu L**, Han S, Liu Y, Wang H, Yang Y, Qiu F, Peng W, Tang L, Fu J, Zhu XF, Ding X, Zhu Y. The influence of immunosuppressants on the fertility of males who undergo renal transplantation and on the immune function of their offspring. *Transpl Immunol* 2009; **22**: 28-31 [PMID: 19818850 DOI: 10.1016/j.trim.2009.10.001]
51 **Ligumsky M**, Badaan S, Lewis H, Meirow D. Effects of 6-mercaptopurine treatment on sperm production and reproductive performance: a study in male mice. *Scand J Gastroenterol* 2005; **40**: 444-449 [PMID: 16028439]
52 **Rajapakse RO**, Korelitz BI, Zlatanic J, Baiocco PJ, Gleim GW. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 684-688 [PMID: 10710057]
53 **Nørgård B**, Pedersen L, Jacobsen J, Rasmussen SN, Sørensen HT. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; **19**: 679-685 [PMID: 15023170 DOI: 10.1111/j.1365-2036.2004.01889.x]
54 **Francella A**, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003; **124**: 9-17 [PMID: 12512024 DOI: 10.1053/gast.2003.50014]
55 **Teruel C**, López-San Román A, Bermejo F, Taxonera C, Pérez-Calle JL, Gisbert JP, Martín-Arranz M, Ponferrada A, Van Domselaar M, Algaba A, Estellés J, López-Serrano P, Linares PM, Muriel A. Outcomes of pregnancies fathered by inflammatory bowel disease patients exposed to thiopurines. *Am J Gastroenterol* 2010; **105**: 2003-2008 [PMID: 20700117 DOI: 10.1038/ajg.2010.138]
56 **Akbari M**, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 15-22 [PMID: 22434610 DOI: 10.1002/ibd.22948]
57 **Saxena AK**, Dhungel S, Bhattacharya S, Jha CB, Srivastava AK. Effect of chronic low dose of methotrexate on cellular proliferation during spermatogenesis in rats. *Arch Androl* 2004; **50**: 33-35 [PMID: 14660169]
58 **Shrestha S**, Dhungel S, Saxena AK, Bhattacharya S, Maskey D. Effect of methotrexate (MTX) administration on spermatogenesis: an experimental on animal model. *Nepal Med Coll J* 2007; **9**: 230-233 [PMID: 18298010]
59 **Sussman A**, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215-217 [PMID: 7356357]
60 **El-Beheiry A**, El-Mansy E, Kamel N, Salama N. Methotrexate and fertility in men. *Arch Androl* 1979; **3**: 177-179 [PMID: 518200]
61 **Weber-Schoendorfer C**, Hoeltzenbein M, Wacker E, Meister R, Schaefer C. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. *Rheumatology* (Oxford) 2014; **53**: 757-763 [PMID: 24369411 DOI: 10.1093/rheumatology/ket390]
62 **Blackburn WD**, Alarcón GS. Impotence in three rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1989; **32**: 1341-1342 [PMID: 2803334 DOI: 10.1002/ anr.1780321029]
63 **Riba N**, Moreno F, Costa J, Olive A. [Appearance of impotence in relation to the use of methotrexate]. *Med Clin* (Barc) 1996; **106**: 558 [PMID: 8656751]
64 **Thomas E**, Koumouvi K, Blotman F. Impotence in a patient with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 2000; **27**: 1821-1822 [PMID: 10914881]
65 **Masuda H**, Fujihira S, Ueno H, Kagawa M, Katsuoka Y, Mori H. Ultrastructural study on cytotoxic effects of cyclosporine A in spermiogenesis in rats. *Med Electron Microsc* 2003; **36**: 183-191 [PMID: 14505063 DOI: 10.1007/s00795-003-0213-4]
66 **Bouloux PM**, Wass JA, Parslow JM, Hendry WF, Besser GM. Effect of cyclosporin A in male autoimmune infertility. *Fertil Steril* 1986; **46**: 81-85 [PMID: 3720982]
67 **Sakamoto Y**, Matsumoto T, Kumazawa J. Cell-mediated autoimmune response to testis induced by bilateral testicular injury can be suppressed by cyclosporin A. *J Urol* 1998; **159**: 1735-1740 [PMID: 9554403 DOI: 10.1097/00005392-199805000-00103]
68 **Haberman J**, Karwa G, Greenstein SM, Soberman R, Glicklich D, Tellis V, Melman A. Male fertility in cyclosporine-treated renal transplant patients. *J Urol* 1991; **145**: 294-296 [PMID: 1988720]
69 **Treacy G**. Using an analogous monoclonal antibody to evaluate the reproductive and chronic toxicity potential for a humanized

anti-TNFalpha monoclonal antibody. *Hum Exp Toxicol* 2000; **19**: 226-228 [PMID: 10918512]
70 **Mahadevan U**, Terdiman JP, Aron J, Jacobsohn S, Turek P. Infliximab and semen quality in men with inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 395-399 [PMID: 15803031 DOI: 10.1097/01.MIB.0000164023.10848.c4]
71 **Villiger PM**, Caliezi G, Cottin V, Förger F, Senn A, Østensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. *Ann Rheum Dis* 2010; **69**: 1842-1844 [PMID: 20610443 DOI: 10.1136/ard.2009.127423]
72 **Ramonda R**, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M, Pizzol D, Punzi L, Garolla A. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. *Fertil Steril* 2014; **101**: 359-365 [PMID: 24332378 DOI: 10.1016/j.fertnstert.2013.10.048]
73 **Paschou S**, Voulgari PV, Vrabie IG, Saougou IG, Drosos AA. Fertility and reproduction in male patients with ankylosing spondylitis treated with infliximab. *J Rheumatol* 2009; **36**: 351-354 [PMID: 19040305 DOI: 10.3899/jrheum.080554]
74 **Puchner R**, Danninger K, Puchner A, Pieringer H. Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception. *Clin Exp Rheumatol* 2012; **30**: 765-767 [PMID: 22935608]
75 **Sarkar O**, Bahrainwala J, Chandrasekaran S, Kothari S, Mathur PP, Agarwal A. Impact of inflammation on male fertility. *Front Biosci* (Elite Ed) 2011; **3**: 89-95 [PMID: 21196288 DOI: 10.2741/e223]
76 **Timmer A**, Bauer A, Dignass A, Rogler G. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. *Clin Gastroenterol Hepatol* 2007; **5**: 87-94 [PMID: 17234557 DOI: 10.1016/j.cgh.2006.10.018]
77 **El-Tawil AM**. Zinc deficiency in men with Crohn's disease may contribute to poor sperm function and male infertility. *Andrologia* 2003; **35**: 337-341 [PMID: 15018135]
78 **Owczarek D**, Rodacki T, Domagała-Rodacka R, Cibor D, Mach T. Diet and nutritional factors in inflammatory bowel diseases. *World J Gastroenterol* 2016; **22**: 895-905 [PMID: 26811635 DOI: 10.3748/wjg.v22.i3.895]
79 **Swanson GR**, Sedghi S, Farhadi A, Keshavarzian A. Pattern of alcohol consumption and its effect on gastrointestinal symptoms in inflammatory bowel disease. *Alcohol* 2010; **44**: 223-228 [PMID: 20682190 DOI: 10.1016/j.alcohol.2009.10.019]
80 **Jowett SL**, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, Welfare MR. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut* 2004; **53**: 1479-1484 [PMID: 15361498]
81 **Kalyani R**, Basavaraj PB, Kumar ML. Factors influencing quality of semen: a two year prospective study. *Indian J Pathol Microbiol* 2007; **50**: 890-895 [PMID: 18306599]
82 **Emanuele MA**, Emanuele NV. Alcohol's effects on male reproduction. *Alcohol Health Res World* 1998; **22**: 195-201 [PMID: 15706796]
83 **Sharma R**, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod Biol Endocrinol* 2013; **11**: 66 [PMID: 23870423 DOI: 10.1186/1477-7827-11-66]
84 **Cosnes J**. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol* 2004; **18**: 481-496 [PMID: 15157822]
85 **Zenzes MT**. Smoking and reproduction: gene damage to human gametes and embryos. *Hum Reprod Update* 2000; **6**: 122-131 [PMID: 10782570]
86 **Sharma R,** Harlev A, Agarwal A, Esteves SC. Cigarette Smoking and Semen Quality: A New Meta-analysis Examining the Effect of the 2010 World Health Organization Laboratory Methods for the Examination of Human Semen. *Eur Urol* 2016; Epub ahead of print [PMID: 27113031 DOI: 10.1016/j.eururo.2016.04.010]
87 **Andrews JM**, Mountifield RE, Van Langenberg DR, Bampton PA, Holtmann GJ. Un-promoted issues in inflammatory bowel disease: opportunities to optimize care. *Intern Med J* 2010; **40**: 173-182 [PMID: 19849744 DOI: 10.1111/j.1445-5994.2009.02110.x]
88 **Mountifield R**, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. *Inflamm Bowel Dis* 2009; **15**: 720-725 [PMID: 19067431 DOI: 10.1002/ibd.20839]

P- Reviewer: Inoue T, Kellermayer R, Sinha R **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com