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TOPIC HIGHLIGHT

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## Inflammatory bowel diseases and human reproduction: A comprehensive evidence-based review

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### Abstract

To evaluate the effects of inflammatory bowel diseases (IBDs) on human reproduction, we reviewed the current literature using a systematic search for published studies (articles and/or abstracts) without limits for English language. We searched on Medline (through PubMed), the Institute for Scientific Information, the Web of Science and the websites for the registration of controlled trials (<http://controlled-trials.com/>). Bib-

liographies of retrieved articles, books, expert opinion review articles and reviewed bibliographies from subject experts were manually searched. Titles and abstracts were screened initially, and potential relevant articles were identified and reviewed. Whenever possible, data were analyzed by comparing IBD patients *vs* healthy controls, and patients with active IBDs *vs* those with disease in remission. The effects of IBDs on female fertility, fertility in infertile couples, pregnancy and male infertility were examined separately. Patients with IBDs in remission have normal fertility. At the moment, there is no established guideline for the preservation of fertility in women with IBD undergoing surgery. Further data are needed regarding guidelines for the management of these patients. Data regarding IBDs and infertility are currently completely lacking. Considering the prevalence of intestinal pathology in young adults of childbearing age, this field is of great scientific and clinical interest, opening up important future perspectives. Another important and as yet unexplored point is the response to treatments for infertility in patients with IBDs. In particular, the question is whether the reproductive outcomes (clinical and biological) can be influenced by the IBD of one of the partners. The goals for successful reproductive outcomes in IBD population are correct counseling and disease remission. IBDs significantly affect several reproductive aspects of human (female, male, couple) reproduction. Further data are needed to develop guidelines for the clinical management of subjects of reproductive age with IBDs.

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**Key words:** Inflammatory bowel diseases; Fertility; Infertility; Pregnancy

**Core tip:** The current comprehensive evidence-based review evaluated the most recent data regarding the

## effects of inflammatory bowel diseases on human reproduction.

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## INTRODUCTION

Inflammatory bowel diseases (IBDs) predominantly affect younger patients of reproductive age. To date, several reviews<sup>[1-4]</sup> have been published in the English literature whose aim was to evaluate and clarify the impact on obstetric outcomes of both the IBDs themselves and the drugs commonly used to treat them. However, very little is known on the overall effect of IBDs on human reproduction.

The study of human reproduction includes not only the effects of IBDs and their treatment on pregnancy but also their effects on the menstrual cycle and hormonal patterns, on the subfertile women scheduled for ovulation induction cycles or assisted reproductive techniques (ARTs), on future reproductive potential in younger and/or adolescent women, and on male fertility, including data on semen parameters and libido/hormonal patterns.

Based on these considerations, the current study was designed to provide an evidence-based overview on the effects of IBDs on all aspects of human reproduction, including both female and male fertility, and to provide a critical synthesis useful for clinical practice.

## SEARCH STRATEGY

To obtain evidence-based data and to provide evidence-based recommendations, a systematic search for studies (articles and/or abstracts), without English language limitation, was performed.

It included the combination of the following medical subject headings or keywords: “assisted reproduction techniques”, “ART”, “Crohn’s disease”, “complication”, “effectiveness”, “efficacy”, “embryo”, “endometrium”, “fertility”, “fetal”, “foetal”, “infertility”, “inflammatory bowel disease(s)”, “IBD(s)”, “intracytoplasmic insemination”, “ICSI”, “*in vitro* fertilization”, “IVF”, “libido”, “management”, “menstrual cycle”, “menses”, “neonatal”, “obstetrics”, “ovary”, “pregnancy”, “prevention”, “safety”, “semen analysis”, “sex hormones”, “sperm”, “spermatozoa”, “subfertility”, “surgery”, “therapy”, “treatment”, “UC”, “ulcerative colitis”.

We searched on Medline (through PubMed), the Institute for Scientific Information, the Web of Science, and the websites for the registration of controlled

trials (<http://controlled-trials.com/>). Bibliographies of retrieved articles, books, expert opinion review articles, and reviewed bibliographies from subject experts were manually searched. Titles and abstracts were screened initially, and potentially relevant articles were identified and reviewed.

For each issue, we analyzed mainly meta-analyses and/or randomized controlled trials (RCTs). When meta-analytic data or data from RCTs were lacking, prospective non-randomized and then cohort studies were included in the final analysis.

To construct a comprehensive review, data regarding both primary endpoints, as traditionally suggested by evidence-based medicine (pragmatic view), and intermediate endpoints, crucial to understanding the mechanisms of action (mechanistic view), were extrapolated and analyzed.

Whenever possible, data were analyzed by comparing IBD patients *vs* healthy controls, and patients with active IBDs *vs* those with disease in remission.

## FEMALE FERTILITY

Women with inactive Crohn’s disease (CD) or ulcerative colitis (UC) appear to have normal fertility. In remission, female fertility seems not to be diminished. A case-control study by Elbaz *et al*<sup>[5]</sup> showed that there was an increased need for fertility treatment of women with IBD; however, this association was no longer significant after controlling for maternal age (increasing maternal age is associated with subfertility).

In CD, fertility is normal or slightly reduced<sup>[6-8]</sup>; older referral center studies estimated infertility rates of 32%-42%<sup>[8-11]</sup>, but community-based and population-based studies suggest infertility rates of 5%-14%, similar to that of the general population<sup>[7]</sup>. Women with UC have normal fertility until they undergo surgery<sup>[9,10]</sup>.

Several reasons for the potentially reduced fertility in IBD women have been hypothesized. We have identified two main sources: psychological problems and surgery-related problems.

### Psychological problems

Relatively few data are available regarding sexual dysfunctions in women with IBD. Moody *et al*<sup>[12]</sup> did not find any significant change in rates of dyspareunia and overall frequency of sexual intercourse between women with IBD and matched controls. On the other hand, a mismatch of perception and reality seems to significantly affect family planning decisions in women with IBD. A recent large study<sup>[13]</sup> was published whose aim was to evaluate whether, and to what extent, IBD patients’ perceptions of risk influence their reproductive behavior and to describe IBD patients’ specific concerns related to fertility and pregnancy. “Voluntary childlessness” was the main cause of the reduced fertility rate (number of live births per woman) reported in IBD patients<sup>[13]</sup>. This fear of infertility was most evident in women with CD and pre-

vious surgery<sup>[13]</sup>. In particular, IBD-related reproductive risks seemed to be overestimated by the examined subjects. The main reproductive concerns of IBD patients regarded pregnancy risks, drug-related teratogenicity or toxicity, long-term risks and IBD inheritance<sup>[13]</sup>.

### Surgery-related problems

Women with active CD have decreased fertility<sup>[6]</sup>, perhaps related to the formation of adhesions caused by the disease itself and/or surgery, resulting in tubal infertility<sup>[14]</sup>. Fertility may normalize after induction of remission in women with CD<sup>[15]</sup>. Some surgical procedures, such as rectal excision and pouch formation, appear to have detrimental effects on male and female fertility.

In UC with ileal pouch anal anastomosis (IPAA), the ability to become pregnant is significantly reduced, probably because of the presence of post-surgical adhesions in the pelvis, secondary obstruction of the fallopian tubes or altering the normal tubo-ovarian relationship necessary for ovum capture and transport<sup>[16-18]</sup>. Two studies that evaluated the impact of proctocolectomy with pelvic pouch or end ileostomy on pelvic anatomy, showed that 50 percent of females had complete unilateral or bilateral obstruction of the fallopian tubes<sup>[19,20]</sup>. These studies suggested that pelvic dissection is the likely cause of adhesions and altered pelvic anatomy.

A systematic review showed that IPAA for UC results in decreased fertility<sup>[21]</sup>. The conception rate in women with UC was 40% before IPAA and only 29% after IPAA<sup>[21]</sup>. A meta-analysis estimated that the risk of infertility after IPAA increased by a factor of three<sup>[22]</sup>. The high use of fertility treatments after IPAA compared with other groups illustrates the difficulty these women have in getting pregnant after surgery. Olsen *et al*<sup>[10]</sup> found that after IPAA, 29% of children were born after *in vitro* fertilization compared with only 1% in the general population. Another study<sup>[10]</sup> of Danish and Swedish patients found that females had significantly decreased fecundity (probability of becoming pregnant per month of unprotected intercourse) after IPAA compared with before IPAA. The data regarding fertility after IPAA do not state the number of women who voluntarily chose not to become pregnant and the impact of age on female fertility, which could greatly influence the interpretation of the results.

In a Canadian study, Johnson *et al*<sup>[23]</sup> confirmed that the infertility rate was significantly higher in IPAA patients compared with patients managed non-operatively (38.6% *vs* 13.3%). In that study, the effect of age on the risk of becoming pregnant was investigated for all patients who attempted to become pregnant in both the IPAA and non-operative management groups. There was a negative association between advancing age and success of becoming pregnant: for each additional year of age there was a 12% decrease in the odds of becoming pregnant<sup>[23]</sup>. Increasing age was associated with decreased reproductive ability among all females included in that study<sup>[23]</sup>.

A recent Finnish study showed that, although the probability of a women conceiving in any short time period seemed to be reduced to 47% of the average, the lifetime chance of having at least one live birth after IPAA was 80%<sup>[24]</sup>. Thus, women with IPAA mostly suffer a reduction in the probability of conception rather than complete infertility.

Strategies are needed to improve fertility after IPAA. One possibility would be to perform sub-total colectomy/end ileostomy and delay IPAA, but this would likely be unacceptable to most females. A second strategy would be to preserve tubal patency and normal tubo-ovarian relationship. Various materials are available to prevent post-surgical adhesions in the pelvis; however, as there are no data regarding their efficacy in improving fertility, further research is needed<sup>[25]</sup>.

To date, there are no established guidelines for the preservation of fertility in women with IBD undergoing surgery. However, we believe that an effective strategy should be based on the following principles: (1) proper selection of patients with a specific clinical indication for surgery; (2) proper evaluation of the patient based on factors predictive of ovarian reserve [*i.e.*, age, anti-Müllerian hormone (AMH), antral follicle count]; and (3) surgery that is as minimally destructive of the radical pelvic anatomy as possible.

## FERTILITY IN INFERTILE COUPLES

The purpose of this section is to evaluate the effects of the IBDs in the infertile couple. In particular, our attention focused on reproductive outcomes (*i.e.*, all intermediate steps and final results) of an infertile couple in which one or both partners are affected by IBDs. Both CD and UC mainly affect young adults of reproductive age. Whereas substantial data are available concerning pregnancy in young IBD women or fertility in IBD men, no study has been conducted on IBDs in infertile couples.

In the few last years, only two studies<sup>[26,27]</sup> investigated the ovarian reserve status in CD women, as reflected by serum AMH. The first study<sup>[26]</sup> showed that women with CD do not have severe ovarian reserve alterations compared with a control population. However, age  $\geq$  30 years and a colonic location of the disease could be associated with an accelerated loss of follicles. Another study<sup>[27]</sup> confirmed that serum AMH levels of reproductive-age women with CD were significantly lower compared with the controls, and the Crohn's Disease Activity Index (CDAI) and AMH were inversely correlated. Thus, these data could encourage gastroenterologists to inform CD women of the risk of delaying childbirth.

Finally, only one report<sup>[28]</sup> described the reproductive outcome following intracytoplasmic sperm injection (ICSI) for male factor infertility associated with CD and 6-mercaptopurine (6-MP) chemotherapy. The authors<sup>[28]</sup> reported the first successful birth after ICSI for severe oligozoospermia associated with CD.

## PREGNANCY

Several recent data are available in literature on IBDs and pregnancy. However, the majority of published studies are reviews or retrospective analyses.

### **Effects of pregnancy on IBDs disease activity**

Pregnancy seems to have a beneficial effect on IBD symptoms, especially when it occurs during disease remission. A small, but significant, decrease in the Harvey-Bradshaw index of disease activity during pregnancy, in comparison with the year preceding and following pregnancy, was observed in a retrospective analysis on women with CD<sup>[29]</sup>. Similar results were found in a large European prospective study, showing that 74% of CD and 67% of UC patients with active disease at conception achieved remission later during pregnancy<sup>[30]</sup>.

Factors affecting remission or exacerbation of IBDs have been investigated extensively. In particular, smoking has a negative effect on the course of CD, and some authors showed that the reduced disease activity in pregnancy was partly the result of reduced tobacco smoking during pregnancy<sup>[31]</sup>. By contrast, exacerbation of disease, particularly in the first trimester of pregnancy, could result from discontinuation of maintenance therapy.

The state of the disease at conception is a factor influencing the course of pregnancy<sup>[32-34]</sup>. In fact, patients with active disease at conception often continue to have symptoms during pregnancy, whereas a normal course of pregnancy can be expected in patients who conceive when in remission. In a cohort study with a 10-year follow-up period, it was observed that if conception occurred during remission, the risk of a flare-up was comparable to that in non-pregnant patients with IBD. Instead, when conception occurred during an active disease period, two-thirds of patients relapsed during pregnancy and more than 60% of these patients experienced further deterioration<sup>[35]</sup>.

The course of IBD in the postpartum period remains controversial. A small prospective study reported a decrease in relapse rate in CD, as well as in UC patients, 4 years after pregnancy, in comparison with the 3 years before pregnancy<sup>[36]</sup>. Similarly, in a large cohort study, the yearly flare-up rates decreased from 0.34 to 0.18 in UC and from 0.76 to 0.12 in CD. Two studies<sup>[37,38]</sup> also reported reduced stenosis and resection rates in women with IBD after pregnancy. Mechanisms potentially involved could be related to the hormone relaxin, the effect of pregnancy on the immune response, as well as feto-maternal HLA disparity<sup>[38,39]</sup>. The effects of breastfeeding on flare-up rates in IBD mothers are also controversial<sup>[40,41]</sup>.

### **Effect of IBDs on pregnancy/perinatal outcomes**

Current data indicate that quiescent disease has minimal impact on the course and outcome of pregnancy in IBD patients, whereas patients with active disease at conception have increased rates of spontaneous abortion<sup>[33]</sup> and a significantly increased risk of preterm delivery and low

birth weight<sup>[32,42]</sup>. Overall pregnancy outcomes in women with IBDs (CD or UC) were similar to those of non-IBD pregnant patients<sup>[31]</sup>.

A meta-analysis<sup>[43]</sup>, including 3907 subjects, reported increased risks for preterm delivery (OR = 1.87, 95%CI: 1.52-2.31) in both CD and UC patients; low birth weight (OR = 2.82, 95%CI: 1.42-5.60) in CD but not in UC; and congenital abnormalities (OR = 3.88, 95%CI: 1.14-10.67) in UC but not in CD. A Swedish population study found 4.5% and 1.2% of children born to IBD patients had, respectively, low and very low birth weight, as compared to 2.9% and 0.6% in the overall Swedish population<sup>[44]</sup>. Moser *et al.*<sup>[32]</sup> additionally found an increased incidence of poor maternal weight gain during pregnancy in CD patients with quiescent disease at conception.

In both CD and UC patients, pregnancies ended more frequently with caesarean section compared with the general population<sup>[45]</sup>. Furthermore, pregnant CD and UC patients who needed to be hospitalized had a higher risk of undergoing a caesarean section (OR = 1.72, 95%CI: 1.44-2.04 and OR = 1.29, 95%CI: 1.01-1.66, respectively) in comparison with patients without IBD<sup>[46]</sup>.

### **Prevention and treatment of IBDs during pregnancy**

Most of the drugs used to treat IBD are not associated with increased risk of congenital anomalies or adverse effects on the fetus (Table 1). The 2010 European Crohn's and Colitis Organisation (ECCO) guidelines state "medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risks of medication"<sup>[46]</sup>. Moreover, as complications and adverse pregnancy outcomes mainly occur in patients with active disease, the main concern should be to achieve remission before conception and maintain quiescent disease during pregnancy. Patients who received counseling regarding the benefits and risks of drug treatment before conception and during pregnancy were more likely to remain compliant<sup>[34]</sup>.

It is generally regarded as safe to keep using aminosalicylates (ASA) during pregnancy [Food and Drugs Administration (FDA) category B drug], despite some reports noting a higher incidence of neural tube defects, oral cleft and cardiovascular defects<sup>[47]</sup>. In a recent meta-analysis of treatment of IBD patients with 5-ASA drugs, IBD did not significantly increase the risk of congenital abnormalities (OR = 1.16), stillbirth (OR = 2.38), spontaneous abortion (OR = 1.14), preterm delivery (OR = 1.35) or low birth weight (OR = 0.93)<sup>[48]</sup>.

Several studies<sup>[49,50]</sup> reported that sulfasalazine assumption during pregnancy does not give rise to increased rates of birth defects in women with IBD. Sulfasalazine therapy should be accompanied by extra folate supplementation, as this medication halts folate synthesis by inhibiting dihydrofolate reductase. Folic acid supplementation decreases the augmented risk of oral clefts and cardiovascular anomalies associated with folate antagonist treatment during pregnancy<sup>[51]</sup>. Caution should be applied regarding the use of some mesalamine formulations (*e.g.*,

**Table 1** Safety indications for drugs in pregnancy and breastfeeding

	UC	ECCO rating pregnancy	ECCO rating breastfeeding	Personal observations
5-ASA (except sulfasalazine)	B	Safe	Safe	Avoid high doses for long time, asacol preparations may be switched to another mesalamine
Sulfasalazine	B	Safe	Safe	Folate supplements are required
AZA/6-MP	D	Safe	Probably safe	Discuss breastfeeding with the patient. Avoid lactation in the four hours after intake of the drug
Cyclosporine A	C	Probably safe	Contraindicated	Use only in severe cases of UC to avoid urgent colectomy during pregnancy
Methotrexate	X	Contraindicated	Contraindicated	Discontinue at least 4 mo prior to conception
Corticosteroids	C	Safe	Safe	Very low risk of malformations. If possible, not use for long time
Infliximab	B	Probably safe	Safe	Can be used safely in the first two trimesters of pregnancy. If possible, avoid in the third trimester
Adalimumab	B	Probably safe	No data	Can be used safely in the first two trimesters of pregnancy. If possible, avoid in the third trimester
Metronidazole	B	Probably safe	Best avoided	Very slight increase of cleft lip. Use only if strictly necessary
Ciprofloxacin	C	Probably safe	Probably safe	Use only for short periods and avoid in the first trimester
Thalidomide	X	Contraindicated	Contraindicated	

5-ASA: 5-aminosalicylates; AZA: Azathioprine; 6-MP: 6-mercaptopurine; ECCO: European Crohn's Colitis Organisation; UC: Ulcerative colitis.

asacol) that contain dibutyl phthalate (DBP) as a coating agent. The use of DBP-coated medications produces measurable phthalate metabolite levels in urine. Prenatal exposure to DBP can cause congenital malformations in the male urogenital tract<sup>[52]</sup>. Finally, the sulfasalazine metabolite sulfapyridine is secreted into breast milk. ASA are generally considered safe during lactation, although a case of bloody diarrhea in an infant has been reported<sup>[53-55]</sup>.

The use of antibiotics during pregnancy, *i.e.*, macrolides and quinolones, should be considered with caution. Metronidazole is considered a low-risk drug during pregnancy (FDA class B). While several studies did not find an association between metronidazole treatment and birth defects<sup>[56]</sup>, a large case-control study showed an increased incidence of cleft lip and/or cleft palate in infants of mothers exposed to metronidazole in the first trimester of pregnancy<sup>[57]</sup>. Thus, it should be limited to short-term use for the treatment of pouchitis. In addition, as metronidazole is excreted in breast milk, breastfeeding during its administration is not recommended<sup>[56]</sup>.

Quinolone antibiotics are FDA category C drugs and should be avoided because they carry an increased risk of arthropathy because of their high affinity for bone and cartilage. ECCO recommends avoiding quinolone use in the first trimester of pregnancy<sup>[57]</sup>. Data on breastfeeding are limited, but quinolone use is probably compatible with breastfeeding<sup>[58,59]</sup>.

The recent London position statement on biological therapy for IBD states that anti-tumor necrosis factor (TNF) therapy is considered low risk and can be used in the preconception period and during the first two trimesters of pregnancy<sup>[60]</sup>. The cytokine TNF- $\alpha$  not only plays a pivotal role in the inflammation process underlying IBD, but also plays physiological roles in host defense mechanisms and pregnancy. During pregnancy, TNF- $\alpha$  probably plays a role in protecting the fetus against teratogenic stress<sup>[61]</sup>. Despite the role of TNF in pregnancy, treatment with anti-TNF antibodies can be considered

safe in the preconception period and the first part of pregnancy, because IgG antibodies do not cross the placenta in the first pregnancy trimester and transplacental IgG transport mainly takes place during the late second and third trimester of pregnancy<sup>[62,63]</sup>. Maternal transfer of IgG during the last trimester of pregnancy provides the neonate with sufficient acquired immunity to defend itself while its own immune system is becoming fully functional.

The currently available TNF inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab) are all classified as FDA category B drugs, indicating that no teratogenic effects of these drugs were observed in animal reproduction studies; however, adequate and controlled human safety data are still lacking. Transfer of anti-TNF antibodies to the fetus during the last part of pregnancy may mean exposure of the neonate in the first months after birth, raising potential concerns about infection and response to vaccines<sup>[60]</sup>.

Infants exposed to immunosuppressive drugs during pregnancy probably should be considered to be immunocompromised, as are their mothers. ECCO guidelines state that live vaccinations (BCG, rotavirus, mumps-measles-rubella (MMR) and varicella zoster) are contraindicated until exposure to immunosuppressants has been discontinued for at least 3 mo<sup>[64]</sup>. IgA is the predominant immunoglobulin in human milk, so secretion of TNF inhibitors in milk is likely to be very limited and breastfeeding under anti-TNF treatment can be considered safe<sup>[65]</sup>.

Natalizumab is an  $\alpha$ -4 integrin inhibitor approved for treatment of CD in the US, but not in Europe. Experience with natalizumab in the context of IBD is still limited, even if this biological compound is widely used for treating multiple sclerosis. It has received an FDA category C label. Thus, at present insufficient data are available to reach a definite conclusion on the safety of natalizumab during pregnancy and lactation.

Corticosteroids are FDA category C drugs. They are

believed to be safe throughout pregnancy at doses up to 15 mg per day<sup>[60]</sup>, whereas higher doses increase the risk of infection and premature delivery<sup>[66]</sup>. Systemic treatment with corticosteroids during the first trimester of pregnancy was found to slightly increase the risk of oral clefts (OR = 3.35, 95%CI: 1.97-5.69), while the overall risk of congenital malformations is not significantly increased (OR = 1.45, 95%CI: 0.80-2.60)<sup>[67]</sup>.

Pregnant women are preferably treated with prednisone or prednisolone, as the bulk of these compounds are inactivated by placental 11 $\beta$ -hydroxy steroid dehydrogenase, the physiological mechanism in place to protect the fetus from elevated maternal cortisol levels during pregnancy. Treatment with corticosteroids is compatible with breastfeeding<sup>[68,69]</sup>.

Cyclosporine crosses the placenta but is rapidly cleared in the neonate and has no known teratogenic effect. FDA categorizes cyclosporine in pregnancy category C for lack of controlled studies in humans; however, cyclosporine does not appear to be a major teratogen.

A meta-analysis<sup>[58]</sup> on the use of cyclosporine in pregnancy showed that cyclosporine use in pregnancy was not associated with major malformations, but slightly decreased birth weight and duration of gestation. In IBD patients, cyclosporine use in refractory UC during pregnancy has been shown to be safe and effective. Its main use in pregnant IBD patients is the prevention of urgent colectomy in fulminant UC<sup>[70,71]</sup>.

Although a number of cases are reported where no overt adverse effects were observed in breastfed infants of mothers treated with cyclosporine, the use of this drug during lactation is generally not advised as cyclosporine is secreted in milk at high concentrations, leading to potential nephrotoxicity and immunosuppression in exposed infants<sup>[72]</sup>.

ASA and 6-MP are still designated as FDA category D drugs, indicating that increased risk for the fetus exists, but the risk must be weighed against the possible benefits of the drug. A recent Danish cohort study showed an increased risk of preterm delivery and low birth weight in women exposed to azathioprine (AZA) or 6-MP during pregnancy, but no significant increase in congenital malformations<sup>[50]</sup>.

The CESAME study<sup>[73]</sup>, a cohort study comparing IBD patients exposed to thiopurine therapy during pregnancy with women receiving other treatments or women without any drug therapy, showed that thiopurine exposure was not associated with low birth weight prematurity and congenital abnormalities, but was associated with preterm birth. Exposure in men at the time of conception was not associated with congenital abnormalities<sup>[74]</sup>. Thiopurine treatment is generally considered a contraindication for breastfeeding.

Methotrexate has teratogenic properties and is contraindicated during pregnancy (FDA category X). Methotrexate metabolites have long tissue half-lives; therefore, its administration must be stopped 3 to 6 mo before conception<sup>[75]</sup>. Folic acid supplementation after methotrexate

withdrawal is also recommended because methotrexate acts as a folate antagonist. Methotrexate is also contraindicated during lactation because of its potential accumulation in the child's tissues.

Thalidomide and its analog lenalidomide partly counteract the effects of TNF- $\alpha$  and have been used in patients with refractory CD, even if currently available systematic evidence does not clearly demonstrate the benefit of these drugs<sup>[76]</sup>. The teratogenicity of these drugs has been well documented, indicating increased risks for limb defects, central nervous system defects, and congenital abnormalities in the cardiovascular, respiratory, gastrointestinal, and genitourinary tracts. Thus, thalidomide is absolutely contraindicated in pregnancy (FDA category X) and patients taking thalidomide are advised to use two complementary contraceptive methods<sup>[77,78]</sup>. Although lenalidomide appears less teratogenic in animal studies, the lack of studies demonstrating its safety in humans leads to the absolute contraindication of this drug in pregnant patients or in patients wishing to become pregnant<sup>[77,78]</sup>.

### **Management of delivery in women with IBDs**

Pregnancy should not be considered high risk in all cases of IBDs. Delivery, therefore, can be carried out in clinics of the second or third level. Only patients with active IBD necessitating steroid and/or anti-TNF treatment, patients with ileostomies, and patients with ileoanal pouches should be referred to high-risk pregnancy clinics.

Active perianal disease at the time of delivery is an indication for caesarean section, whereas patients without history of perianal disease or inactive perianal disease do not require caesarean delivery<sup>[45]</sup>. In UC patients with IPAA, caesarean section rates of almost 50% have been reported, but the incidence of pouch-related complications was low and pouch function was found to be unrelated to the mode of delivery<sup>[79]</sup>. However, the most recent ECCO guidelines state that the presence of an ileoanal pouch in CD patients is an indication for caesarean section<sup>[80]</sup>. Moreover, patients with IPAA surgery in the past are always advised to have caesarean section, and we recommend that an abdominal surgeon should be present during the surgery.

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## **MALE FERTILITY**

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### **Clinical data**

Infertility in men with IBD has been relatively less studied than infertility in women with IBD. A recent European consensus states that both male and female fertility are not significantly affected in non-operated IBD patients when disease is quiescent, compared to the general population<sup>[81]</sup>. It is important to note that IBD patients remain voluntarily childless more frequently than non-IBD controls<sup>[82]</sup>. In a survey among 255 Australian IBD patients, fear concerning IBD heritability, side effects of the medication on the child, and medical advice given by physicians were the most important reasons for voluntary childlessness<sup>[13]</sup>.

**Table 2** Effects of inflammatory bowel disease medications on erectile dysfunction, male infertility and partner's pregnancy

	Erectile dysfunction	Infertility	Pregnancy complications	Recommendations
5-ASA (except sulfasalazine)	No	Single reversible case	No reports	No recommendations to discontinue prior to conception
Sulfasalazine	Single case	Yes, reversible, not dose dependent	One study	Switch to other 5-ASA preparations
AZA/6-MP	No reports	No	Controversial	No recommendations to discontinue prior to conception
Cyclosporine A	No reports	No	No reports	No recommendations to discontinue prior to conception
Methotrexate	Yes	Controversial	No reports	Discontinue 3-4 mo prior to conception
Steroids	No reports	No	No reports	Lack of data to discontinue
TNF- $\alpha$ inhibitors (infliximab, and only a case report for adalimumab)	No reports	Reduce sperm quality, but no infertility	No	No recommendations to discontinue prior to conception, but barrier methods during pregnancy

5-ASA: 5-aminosalicylates; AZA: Azathioprine; 6-MP: 6-mercaptopurine; TNF: Tumor necrosis factor.

A recent systematic review<sup>[83]</sup> on fertility in non-surgically treated IBD showed that in men with CD (a total of 493 men in two population-based and one referral center studies), there was an 18%-50% reduction in fertility compared with controls, although whether the cause was involuntary infertility or voluntary childlessness was not indicated. There was no evidence of reduced fertility in men with UC<sup>[83]</sup>.

#### **IBD and male fertility intermediate end-points**

Active disease, IBD treatment, and psychological factors affect male reproductive and sexual function<sup>[84]</sup>. Most male IBD patients considered "maintaining remission" as important at conception<sup>[85]</sup> and in fact inflammation has a negative effect on male fertility<sup>[86]</sup>. Men who were in remission or who had only mild disease activity had rates of erectile dysfunction similar to those of healthy control subjects, whereas men with more severe IBD activity had higher rates<sup>[87]</sup>.

#### **IBD and semen parameters**

There are no large studies that assess semen abnormalities in IBD patients on no medication at all. Some studies suggest that factors such as disease activity and nutritional status could affect semen<sup>[88-90]</sup>. Furthermore, there are reports of antisperm antibodies in both men and women with IBD, and these antibodies might contribute to infertility. Antisperm antibodies might be a result of the increased immunological response, caused by increased intestinal permeability, against antigens of gut microbiota possessing common antigenicity with spermatozoa<sup>[91]</sup>. Dimitrova *et al.*<sup>[92]</sup> showed that antisperm antibody incidence in 50 patients with ulcerative colitis was statistically significant compared with 50 healthy blood donors<sup>[92]</sup>. A little study on 10 IBD patients (four women and six men) and reported the presence of antisperm antibodies in semen of male patients and cervical secretions of female patients at the time of ovulation<sup>[93]</sup>.

#### **Surgery and male fertility**

The most common surgery in IBD patients is IPAA.

Proctocolectomy with IPAA has been associated with sexual dysfunction in men. A large study found 1% and 2% of sexual dysfunction at 1 year and 12 years after surgery, respectively<sup>[94]</sup>. Furthermore, 3% of men reported experiencing either retrograde ejaculation or no ejaculation 10 years after surgery<sup>[94]</sup>.

A meta-analysis of 43 observational studies that evaluated patients after IPAA found the pooled incidence of sexual dysfunction to be 3.6%<sup>[95]</sup>. On the other hand, a study of 122 men who had undergone IPAA evaluated male sexual function using a validated index based on erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction<sup>[96]</sup>. This study showed that, despite any negative effect on erectile function (in particular retrograde ejaculation), the other four features had a statistically significant improvement<sup>[96]</sup>. A Dutch study confirmed that despite an elevated rate of sexual dysfunction of up to 25% in 35 men after IPAA for UC, 90% of patients were satisfied with the operation<sup>[97]</sup>.

A randomized, placebo-controlled trial of sildenafil for erectile dysfunction following rectal excision performed either for cancer or IBD in 32 men showed that post-operative sexual dysfunction can be treated successfully with sildenafil in most cases (79% of the sildenafil-treated group compared to only 17% of the group taking placebo)<sup>[98]</sup>.

There are other types of surgery beyond IPAA, for example, total colectomy with end ileostomy, colectomy with ileo-rectal anastomosis, and proctocolectomy with ileo-anal anastomosis without a pouch. The reports on sexual function after these procedures are limited, but only ileo-rectal anastomosis avoids the extensive pelvic dissection of the other procedures, which produces adverse effects on sexual function.

#### **Medical treatments and male fertility**

Table 2 shows the effects of IBD medications on erectile dysfunction, infertility and pregnancy. In the general population, medications are responsible for erectile dysfunction in up to 25% of cases<sup>[99]</sup>. The medications used

to treat IBD rarely cause erectile dysfunction; however, antidepressants and anti-anxiety medications, frequently prescribed for patients with IBD, could cause erectile dysfunction because depressive mood negatively influences sexual function (patients with a first diagnosis of IBD had higher rates of depression than patients with diagnosis of colon cancer)<sup>[100]</sup>.

On the other hand, many drugs have been reported to impair semen parameters; sulfasalazine, methotrexate, and infliximab seem to affect sperm quality<sup>[57]</sup>. Of note, confounding factors that could affect male fertility, such as smoking, alcohol consumption, disease status, and medication use, are not always reported in studies investigating the effects of medical treatments on male fertility. Men with IBD rarely have documented physician counseling regarding the potential effects of medication on fertility and pregnancy because gastroenterologists' lack of knowledge of the effects of medications on male fertility or a lack of documentation of their counselling practices<sup>[101]</sup>.

Except for sulfasalazine, the risk of adverse fetal outcomes of other medications must be weighed against the benefit of maintaining good health of the father at the time of conception.

The only 5-ASA medication shown to cause male infertility is sulfasalazine<sup>[102,103]</sup>. Sulfasalazine causes reversible non-dose-dependent semen abnormalities (oligospermia, reduced motility and abnormal morphology)<sup>[104,105]</sup> and infertility in up to 60% of men<sup>[106]</sup>. Impaired sperm maturation and oxidative stress from the sulfapyridine constituent of the drug are thought to be the cause<sup>[107-110]</sup>. Male fertility is restored two months after sulfasalazine withdrawal or switching to other mesalazine preparations<sup>[111-115]</sup>. A single case of impotence was reported that was resolved after switching to olsalazine<sup>[116]</sup>. One study found an association between sulfasalazine use in men and a higher rate of congenital malformations in their children<sup>[106]</sup>. There is a single case report of mesalazine-induced oligospermia and infertility that reversed when the drug was stopped<sup>[117]</sup>. Given these data, no recommendations are made to discontinue 5-ASA (except sulfasalazine) for men planning to conceive.

A study of 18 men with IBD showed that AZA did not reduce semen quality, and thus male fertility, in IBD: no changes in semen parameters were noted after 11 ± 5 mo of AZA administration or during long-term treatment (49 ± 14 mo)<sup>[118]</sup>. In a survey of 164 male renal transplant patients, long-term therapy with cyclosporine, AZA and prednisone demonstrated no effects on fertility<sup>[119]</sup>.

The teratogenic effect of AZA and its metabolite 6-MP remains controversial. In one retrospective study, the incidence of pregnancy-related complications was significantly increased when the fathers used 6-MP within 3 mo of conception<sup>[120]</sup>. Specifically, in men with IBD under 6-MP, congenital anomalies and spontaneous abortions were detected in 4% and 6% of cases, respectively. These data are substantially different from those ob-

served in men with IBD who were not taking this drug (no congenital anomalies and 2% of spontaneous abortions)<sup>[120]</sup>. However, the rates of congenital abnormalities and spontaneous abortions were below those of the general population - 3% and 10%, respectively<sup>[121]</sup>. In a Danish population-based cohort study, the paternal use of AZA or 6-MP before conception was associated with an increased, but not statistically significant, risk of congenital abnormalities<sup>[122]</sup>.

Two other studies did not observe any significant effect of preconception thiopurine exposure of the father on pregnancy outcomes. Francella *et al.*<sup>[123]</sup> showed that there was no statistical difference in conception failures (defined as a spontaneous abortion), abortion secondary to a birth defect, major congenital malformations, neoplasia or increased infections among offspring of male patients taking 6-MP compared with controls. In 2010, Teruel *et al.*<sup>[124]</sup> confirmed there were no significant differences in terms of unsuccessful pregnancies between the exposed group (MP 9, AZA 37) and the control group. Given these data, no recommendations are made to discontinue AZA/6-MP for men planning to conceive.

There are no data regarding the effects of cyclosporine on fertility of men with IBD. In animal models, cyclosporine A causes damage of testicular tissue and sperms<sup>[125]</sup>, but antioxidants may protect from testicular toxicity<sup>[126,127]</sup>. In humans, the small studies conducted do not seem to suggest any association between cyclosporine and male infertility: a decrease in serum antisperm antibodies<sup>[128,129]</sup>, normal semen analysis, and successful pregnancies are described<sup>[130]</sup>. There are no reports of adverse pregnancy among partners of men who were taking cyclosporine. No recommendations are made to discontinue cyclosporine A for men planning to conceive.

Methotrexate is the one most often associated with impotence<sup>[131-133]</sup>. However, few data are available on the effects of methotrexate on male reproductive capability. In animal models, it causes altered spermatogenesis and degeneration of spermatocytes, Sertoli cells, and Leydig cells<sup>[134-136]</sup>. Opinions differ in the literature on the effects of methotrexate on male fertility: the concurrent administration of other chemotherapeutic agents is a limitation<sup>[137]</sup>.

There are small studies reporting on methotrexate use with no other agents. In patients affected by psoriasis, there are cases of documented reversible sterility when the methotrexate was stopped<sup>[138]</sup> and there are several case series that report no change in sperm quality<sup>[139-142]</sup>. There are no reports of adverse pregnancy outcomes among the partners of men exposed to methotrexate before conception<sup>[143]</sup>. However, the active metabolites of methotrexate can remain in cells or tissues for several months after discontinuation<sup>[144]</sup>. Given these data, it is recommended that the drug should be discontinued at least 3-4 mo before attempts at conception for men with IBD<sup>[145-147]</sup>.

Few data are available on the effects of steroid therapy on male fertility<sup>[118,148]</sup>: it appears there is little



impact. Although steroids may inhibit apoptosis of damaged sperm cells, they may prevent pathological excessive apoptosis, which results in oligospermia<sup>[149]</sup>. No recommendations can be made to discontinue steroid use due to insufficient data.

There are few studies also on the effects of anti-tumor necrosis factor agents; the data do suggest, however, that these medications may impair male fertility. Infliximab may also serve to counter the negative effects of TNF- $\alpha$  on sperm quality<sup>[150]</sup>: supraphysiological levels of TNF- $\alpha$  were seen to cause chromatin and DNA damage, and reduce sperm motility<sup>[151]</sup>. Reports on male fertility in ankylosing spondylitis patients showed a decrease in sperm motility in patients on conventional treatment *vs* anti-TNF- $\alpha$ -treated patients<sup>[152]</sup>.

In a study of 10 men, infliximab increased semen volume with a trend towards decreased sperm motility and morphology, but its impact on male fertility was not reported<sup>[153]</sup>. Villinger *et al*<sup>[154]</sup> showed sperm abnormalities that were more pronounced in patients with active spondyloarthritis, but the sperm quality of patients with inactive disease receiving long-term TNF inhibition is comparable to that in healthy controls. Another report on four patients with ankylosing spondylitis who fathered six healthy children during infliximab treatment may provide some reassurance for male patients treated with infliximab<sup>[155]</sup>. The data support continuation of anti-TNF treatment when IBD patients plan fatherhood<sup>[154]</sup>.

The recent Austrian evidence-based consensus on the safe use of infliximab in inflammatory bowel disease<sup>[156]</sup> states that infliximab may lead to reduced quality by decreasing sperm motility and affecting sperm morphology, although these findings do not demonstrate that male fertility would be reduced<sup>[157]</sup>.

Infliximab treatment of men prior to planned conception does not seem to cause embryo toxicity. For anti-TNF alpha, as it is unknown whether the fetus will be affected by exposure to anti-TNF alpha through semen, the ECCO consensus on reproduction in IBD advises barrier methods during pregnancy. Data on the impact of other biologicals on male fertility are currently lacking, although there is a case report of 35-year-old father of a healthy 4-year-old child who was successfully treated for 3 years with adalimumab for ankylosing spondylitis<sup>[158]</sup>. No recommendations are made to discontinue anti-TNF- $\alpha$  treatment for men planning to conceive.

## CONCLUSION

IBDs significantly affect several reproductive aspects of human (female, male, couple) reproduction. Moreover, further data are needed in order to develop guidelines for the clinical management of subjects of reproductive age with IBDs. In fact, at the moment, there are no established guidelines for the preservation of fertility in women with IBD undergoing surgery. Further data are needed regarding the management of these patients.

Data regarding IBDs and infertility are currently com-

pletely lacking. Considering the prevalence of intestinal pathology in young adults of childbearing age, this field is of great scientific and clinical interest, opening up important future perspectives. Further studies should, in fact, be conducted to determine whether the treatments for infertility have an effect on the state of IBD (remission, flare-up, recurrence). Another important point as yet unexplored is the response to treatments for infertility in patients with IBDs. In particular, the question is whether the reproductive outcomes (clinical and biological) can be influenced by the IBD of one of the partners.

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