**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 7620**

**Columns: TOPIC HIGHLIGHT**

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

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

Palomba S *et al*. Inflammatory bowel diseases and reproduction

Stefano Palomba, Giuliana Sereni, Angela Falbo, Marina Beltrami, Silvia Lombardini, Maria Chiara Boni, Giovanni Fornaciari, Romano Sassatelli, Giovanni Battista La Sala

**Stefano Palomba, Angela Falbo, Giovanni Battista La Sala,** Obstetrics and Gynecology Unit, Department of Obstetrics, Gynecology and Pediatrics, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, 42123 Reggio Emilia, Italy

**Giuliana Sereni, Romano Sassatelli,** Gastroenterology and Digestive Endoscopy Unit, Gynecology and Pediatrics, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, 42123 Reggio Emilia, Italy

**Marina Beltrami, Silvia Lombardini, Maria Chiara Boni, Giovanni Fornaciari,** Department of Medicine and Gastroenterology, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, 42123 Reggio Emilia, Italy

**Giovanni Battista La Sala,** Department of Obstetrics and Gynecology, University of Modena and Reggio Emilia, 41124 Modena, Italy

**Author contributions:** Palomba S, Sereni G, Fornaciari G, and La Sala GB designed the research; Falbo A, Beltrami M, Lombardini S, Boni MC,and Sassatelli R performed the research; Palomba S, Sereni G and Fornaciari G wrote the paper.

**Correspondence to: Stefano Palomba, MD**, Obstetrics and Gynecology Unit, Department of Obstetrics, Gynecology and Pediatrics, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Viale Risorgimento 80, 42123 Reggio Emilia, Italy. [stefanopalomba@tin.it](mailto:stefanopalomba@tin.it)

**Telephone:** +39-3-475880503 **Fax:** +39-9-611910602

**Received:** November 26, 2013 **Revised:** February 13, 2014

**Accepted:** February 26, 2014

**Published online:**

**Abstract**

To evaluate the effects of inflammatory bowel diseases (IBDs) on human reproduction. Review of the current literature through 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 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 initially screened, and potential relevant articles were identified and reviewed. Whenever possible, data were analyzed comparing IBD patients versus healthy controls and patients with active IBDs versus 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 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. The goals for successful reproductive outcomes in IBD population are correct counselling and disease remission. IBDs significantly affect several reproductive aspects of human (female, male, couple) reproduction. Further data are needed in order to develop guidelines for the clinical management of subjects with IBDs in reproductive age.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**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.

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.

**Available from: URL:**

**DOI:**

**INTRODUCTION**

Inflammatory bowel diseases (IBDs) predominantly affect younger patients that are in their reproductive age. To date, there are several reviews[1-4] available 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 employed for their treatment. However, very little is known on the overall effect of IBDs on human reproduction.

In fact, the study of human reproduction includes not only the effects of IBDs and their treatment on pregnancy but also their effects on menstrual cyclicity and hormonal pattern, 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 on libido/hormonal pattern.

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 a critical synthesis useful for clinical practice.

**SEARCH STRATEGY**

In order to obtain evidence-based data and to give evidence-based recommendations, a systematic research for studies (articles and/or abstracts) without limits for English language 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)”, “intracytosplasmic 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”, “ulcerative colitis”, “UC”.

We searched on Medline (through PubMed), the Institute for Scientific Information 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 initially screened, and potential 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.

In order 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 comparing IBD patients versus healthy controls and patients with active IBDs versus 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*[5] showed that the need for fertility treatment of women with IBD was increased but this association was no longer significant after controlling for maternal age (it is well known that increasing maternal age is associated with subfertility).

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

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*[12] 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[13] was published whose aim was to evaluate whether, and to what extent, IBD patients’ perceptions of risk influence their reproductive behaviour 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[13]. This fear of infertility was most evident in women with CD and previous surgery[13]. In particular, IBD-related reproductive risks seemed to be overestimated by examined subjects. The main reproductive concerns in IBD patients regarded pregnancy risks, drug-related teratogenicity or toxicity, long-term risks, and IBD inheritance[13].

***Surgery-related problems***

Women with active CD have increased infertility[6], perhaps related to the formation of adhesions caused by the disease itself and/or surgery, resulting in tubal infertility[14]. Fertility may normalise after induction of remission in women with CD[15]. 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 due to the presence of post-surgical adhesions in the pelvis and secondary obstruction of the fallopian tubes or altering the normal tubo-ovarian relationship necessary for ovum capture and transport[16-18]. 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[19-20]. These studies suggest 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[21]. The conception rate in women with UC was 40% before IPAA and only 29% after IPAA[21]. A meta-analysis estimated that the risk of infertility after IPAA increased by a factor of three[22]. 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*[10] found that after IPAA, 29% of children were born after in vitro fertilization compared with only 1% in the general population. Another study[10] 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*[23] confirm that infertility rate was significantly higher in the IPAA patients compared with the patients managed non-operatively (38.6% *vs* 13.3%). In this study, the effect of age on the risk of becoming pregnant was investigated for all patients who attempted to become pregnant in both 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[23]. Increasing age was associated with decreased reproductive ability among all females included in this study[23].

A recent Finnish study shows 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%[24]. 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 measures to preserve tubal patency and normal tubo-ovarian relationship. Various materials are available to prevent post- surgical adhesions in the pelvis, but as there are no data regarding their efficacy in improving fertility, further research is needed[25].

To date, there is no established guideline 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 is 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[26,27] investigated the ovarian reserve status in CD women, as reflected by serum AMH. The first study[26] showed that women with CD do not have severe ovarian reserve alterations compared to a control population. However, age ≥ 30 years and a colonic location of the disease could be associated with an accelerated loss of follicles. One study[27] confirmed that serum AMH levels of reproductive-age women with CD were significantly lower compared to the controls, and 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[28] described the reproductive outcome following intracytoplasmic sperm injection (ICSI) for male factor infertility associated with CD and 6-mercaptopurine chemotherapy. The authors[28] 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 the pregnancy was observed in a retrospective analysis on women with CD[29]. 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[31].

Factors affecting remission or exacerbation of IBDs have been extensively investigated. 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 due to reduced tobacco smoking during pregnancy[31]. On the contrary, exacerbation of disease, particularly in the first trimester of pregnancy, could be due to discontinuation of maintenance therapy.

The state of the disease at conception has been demonstrated to be a factor influencing the course of pregnancy[31-34]. 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 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[35].

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[36]. Similarly, in a large cohort study, the yearly flare rates decreased from 0.34 to 0.18 in UC and from 0.76 to 0.12 in CD. Two studies [37,38] 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[38,39]. The effects of breastfeeding on flare rates in IBD mothers is also controversial[40,41].

***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[33] and a significantly increased risk of preterm delivery and low birth weight[32,42]. A large European prospective study concluded that overall pregnancy outcomes in women with IBDs (CD or UC) were similar to those of non-IBD pregnant patients[31].

A further meta-analysis[43] 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[44]. Moser *et al*[32] 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 in comparison with the general population[45]. Further, 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[46].

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

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

It is generally regarded as safe to keep using aminosalicylates during pregnancy (FDA category B drug), despite some reports noting a higher incidence of neural tube defects, oral cleft, and cardiovascular defects[47]. In a recent meta-analysis 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) [48].

Several studies[49,50] 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 was shown to decrease the augmented risk of oral clefts and cardiovascular anomalies associated with folate antagonist treatment during pregnancy[51]. Caution should be applied regarding the use of some mesalamine formulations (*e.g.,* 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[52]. Finally, the sulfasalazine metabolite sulfapyridine is secreted into breast milk. Aminosalicylates are generally considered safe during lactation, although a case of bloody diarrhoea in an infant has been reported[53-55].

The use of antibiotics during pregnancy, *i.e.,* matronidaole 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[56], 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[57]. 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[56].

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

The recent London position statement on biological therapy for IBD states that anti-tumour necrosis factor (TNF) therapy is considered low risk and can be used in the preconception period and during the first two trimesters of pregnancy[60]. The cytokine TNF-α not only plays a pivotal role in the inflammation process underlying IBD, but also plays physiological roles in host defence mechanisms and pregnancy. During pregnancy, TNF-α probably plays a role in protecting the foetus against teratogenic stress[61]. 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[62,63]. 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 foetus 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[60].

Infants exposed to immunosuppressive drugs during pregnancy probably should be considered to be immunocompromised, as their mothers are. 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[64]. 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[65].

Natalizumab is an α-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[60], whereas higher doses increase the risk of infection and premature delivery[66]. 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) [67].

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

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 but cyclosporine does not appear to be a major teratogen.

A meta-analysis[58] 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[70,71].

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[72].

Azathioprine and 6-mercaptopurine are still designated as FDA category D drugs, indicating that increased risk for the foetus 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 or 6-mercaptopurine during pregnancy, but no significant increase in congenital malformations[50].

The CESAME study[73], 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[74]. Exposure in men at the time of conception was not associated with congenital abnormalities[74]. Thiopurine treatment is generally considered a contraindication for breastfeeding.

Methotrexate has teratogenic properties and is contraindicated during pregnancy (FDA category X). Since methotrexate metabolites have long tissue half-lives, its administration must be stopped 3 to 6 months before conception[75]. Folic acid supplementation after methotrexate withdrawal is also recommended as 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 analogue lenalidomide partly counteract the effects of TNF-α and have been used in patients with refractory Crohn's disease, even if currently available systematic evidence does not clearly demonstrate the benefit of these drugs[76]. 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[77,78]. 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.

***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 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[45]. 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[79]. However, the most recent ECCO guidelines state that the presence of an ileoanal pouch in CD patients is an indication for caesarean section[80]. Moreover, patients with IPAA surgery in the past are always advised to have caesarean section, and an abdominal surgeon should be present during the surgery.

**MALE FERTILITY**

***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[81]. It is important to note that IBD patients remain voluntarily childless more frequently than non-IBD controls[82]. 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[13].

A recent systematic review 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 as 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 (a total of 217 men in two population-based studies) [83].

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

Active disease, IBD treatment, and psychological factors affect male reproductive and sexual function[84]. Most male IBD patients considered “maintaining remission” as important at conception[85] and in fact inflammation has a negative effect on male fertility[86]. 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[87].

***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[88-90]. 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[91]. Dimitrova showed that antisperm antibody incidence in 50 patients with ulcerative colitis was statistically significant compared to 50 healthy blood donors[92]. Rossato evalueted 10 IBD patients (4 women and 6 men) and reported the presence of antisperm antibodies in semen of male patients and cervical secretions of female patients at the time of ovulation[93].

***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. Furthermore, 3% of men reported experiencing either retrograde ejaculation or no ejaculation 10 years after surgery[94].

A meta-analysis of 43 studies that evaluated patients after IPAA found the pooled incidence of sexual dysfunction to be 3.6%[95]. 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. This study showed that, despite any negative effect on erectile function (in particular retrograde ejaculation), the other four features had a statistically significant improvement[96]. 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[97].

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) [98].

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 anastamosis 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[99]. The medications used to treat IBD rarely cause erectly 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 first diagnosis of IBD had higher rates of depression than did patients with diagnosis of colon cancer) [100].

On the other hand, many drugs have been reported to impair semen parameters; sulphasalazine, methotrexate, and infliximab seem to affect sperm quality[57]. 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 counselling regarding the potential effects of medication on fertility and pregnancy due to the fact gastroenterologists lack knowledge of the effects of medications on male fertility or to a lack of documentation of their counselling practices[101].

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

**5-ASA:** The only 5-ASA medication shown to cause male infertility is sulfasalazine[102,103]. Sulfasalazine is shown to cause reversible non-dose-dependent semen abnormalities (oligospermia, reduced motility, abnormal morphology) [105,106] and infertility in up to 60% of men[107]. Impaired sperm maturation and oxidative stress due to the sulfapyridine constituent of the drug are thought to be the cause[108-111]. Male fertility is restored two months after sulfasalazine withdrawal or switching to other mesalazine preparations[112-116]. A single case of impotence is reported that was resolved after switching to olsalazine[117]. One study found an association between sulfasalazine use in men and a higher rate of congenital malformations in their children[107]. There is a single case report of mesalazine-induced oligospermia and infertility that reversed when the drug was stopped[104]. Given these data, no recommendations are made to discontinue 5-ASA (except sulfasalazine) for men planning to conceive.

**Azathioprine:** A study of 18 men with IBD showed that azathioprine 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 months) [118]. In a survey of 164 male renal transplant patients, long-term therapy with cyclosporine, azathioprine, and prednisone demonstrated no effects on fertility[119].

The teratogenic effect of azathioprine and its metabolite 6-mercaptopurine remains controversial. In one retrospective study, the incidence of pregnancy-related complications was significantly increased when the fathers used 6-MP within 3 months of conception[120]. 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 observed in men with IBD who were not taking this drug (no congenital anomalies and 2% of spontaneous abortions) [120]. However, the rates of congenital abnormalities and spontaneous abortions were below those of the general population - 3% and 10%, respectively[121]. In a Danish population-based cohort study, the paternal use of azathioprine or mercaptopurine before conception was associated with an increased but not statistically significant risk of congenital abnormalities[122].

Two other studies did not observe any significant effect of preconception thiopurine exposure of the father on pregnancy outcomes. Francella[123] 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[124] confirmed there were no significant differences in terms of unsuccessful pregnancies between the exposed group (mercaptopurine 9, azathioprine 37) and the control group.

Given these data, no recommendations are made to discontinue azathioprine/mercaptopurine for men planning to conceive.

**Cyclosporine A:** There are no data regarding the effects of cyclosporine on fertility of men with IBD. In animal models, it has been demonstrated that cyclosporine A causes damage of testicular tissue and sperms[125]**,** but antioxidants may protect from testicular toxicity[125,126]. In humans, the small studies conducted do not seem to suggest any association between cyclosporine and male infertility: a decrease in serum antisperm antibodies[128,129], normal semen analysis, and successful pregnancies are described[130]. 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:** This drug is the one most often associated with impotence[131-133]. However, few data are available on the effects of methotrexate on male reproductive capability. In animal models, it has been demonstrated to cause altered spermatogenesis and degeneration of spermatocytes, Sertoli cells, and Leydig cells[134-136]. Opinions differ in the literature on the effects of methotrexate on male fertility: the concurrent administration of other chemotherapeutic agents is a limitation[137].

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[138] and there are several case series that report no change in sperm quality[139-142]. There are no reports of adverse pregnancy outcomes among the partners of men exposed to methotrexate before conception[143]. However, the active metabolites of methotrexate can remain in cells or tissues for several months after discontinuation[144]. 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[145-147].

**Steroids:** Few data are available on the effects of steroid therapy on male fertility[118,148]: 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[149]. No recommendations can be made to discontinue steroid use due to insufficient data.

**TNF-alpha inhibitors (Infliximab-Adalimumab):** There are few studies 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-α on sperm quality[150]: supraphysiological levels of TNFα were seen to cause chromatin and DNA damage and reduce sperm motility [151]. Reports on male fertility in ankylosing spondylitis patients showed a decrease in sperm motility in patients on conventional treatment versus anti-TNFα-treated patients[152].

In a study of 10 men, infliximab has been reported to increase semen volume with a trend towards decreased sperm motility and morphology, but its impact on male fertility was not reported[153]. Villinger *et al*[154] showed sperm abnormalities that were more pronounced in patients with active spondyloartrhitis but the sperm quality of patients with inactive disease receiving long-term TNF inhibition is comparable to that in healthy controls. Another report on 4 patients with ankylosing spondylitis who fathered 6 healthy children during infliximab treatment may provide some reassurance for male patients treated with infliximab[155]. The data support continuation of anti-TNF treatment when fatherhood is planned by IBD patients[154].

The recent Austrian evidence-based consensus on the safe use of infliximab in inflammatory bowel disease[156] 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[157].

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 foetus 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[158]. No recommendations are made to discontinue anti-TNFα 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 with IBDs in reproductive age. In fact, 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.Further studies should, in fact, be conducted to determine whether the treatments for infertility have an effect on the state of IBD (remission, flare, 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.

**REFERENCES**

1 **Boregowda G**, Shehata HA. Gastrointestinal and liver disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2013; **27**: 835-853 [PMID: 24207084 DOI: 10.1016/j.bpobgyn.2013.07.006.]

2 **Kane S**. IBD: Activity of IBD during pregnancy. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 571-572 [PMID: 23938453 DOI: 10.1038/nrgastro.2013.152.]

3 **Nielsen OH**, Maxwell C, Hendel J. IBD medications during pregnancy and lactation. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 116-127 [PMID: 23897285 DOI: 10.1038/nrgastro.2013.135]

4 **Selinger CP**. Reproduction in the patient with inflammatory bowel disease. *Minerva Gastroenterol Dietol* 2013; **59**: 285-297 [PMID: 23867948]

5 **Elbaz G**, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. *Int J Gynaecol Obstet* 2005; **90**: 193-197 [PMID: 16043179 DOI: 10.1016/j.ijgo.2005.06.003]

6 **Khosla R**, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. *Gut* 1984; **25**: 52-56 [PMID: 6140209 DOI: 10.1136/gut.25.1.52]

7 **Hudson M**, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997; **58**: 229-237 [PMID: 9252260 DOI: 10.1016/S0020-7292(97)00088-X]

8 **Mayberry JF**, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease: a case control study by European collaborative group. *Gut* 1986; **27**: 821-825 [PMID: 3732892 DOI: 10.1136/gut.27.7.821]

9 **Dubinsky M**, Abraham B, Mahadevan U. Management of the pregnant IBD patient. *Inflamm Bowel Dis* 2008; **14**: 1736-1750 [PMID: 18626967 DOI: 10.1002/ibd.20532]

10 **Olsen KO**, Joelsson M, Laurberg S, Oresland T. Fertility after ileal pouch-anal anastomosis in women with ulcerative colitis. *Br J Surg* 1999; **86**: 493-495 [PMID: 10215821 DOI: 10.1046/j.1365-2168.1999.01076.x]

11 **Fielding JF**. Pregnancy and inflammatory bowel disease. *Ir J Med Sci* 1982; **151**: 194-202 [PMID: 7107181 DOI: 10.1007/BF02940180]

12 **Moody GA**, Mayberry JF. Perceived sexual dysfunction amongst patients with inflammatory bowel disease. *Digestion* 1993; **54**: 256-260 [PMID: 8243839 DOI: 10.1159/000201046]

13 **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]

14 **Arkuran C**, McComb P. Crohn's disease and tubal infertility: the effect of adhesion formation. *Clin Exp Obstet Gynecol* 2000; **27**: 12-13 [PMID: 10758789]

15 **Baiocco PJ**, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* 1984; **6**: 211-216 [PMID: 6144706]

16 **Diamond MP**, Freeman ML. Clinical implications of postsurgical adhesions. *Hum Reprod Update* 2001; **7**: 567-576 [PMID: 11727865 DOI: 10.1093/humupd/7.6.567]

17 **Karande VC**, Pratt DE, Rabin DS, Gleicher N. The limited value of hysterosalpingography in assessing tubal status and fertility potential. *Fertil Steril* 1995; **63**: 1167-1171 [PMID: 7750583]

18 **Seiler JS**. Pelvic pathology affecting fertility. *Int J Fertil* 1987; **32**: 208-212 [PMID: 2885284]

19 **Oresland T**, Palmblad S, Ellström M, Berndtsson I, Crona N, Hultén L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. *Int J Colorectal Dis* 1994; **9**: 77-81 [PMID: 8064194 DOI: 10.1007/BF00699417]

20 **Asztély M**, Palmblad S, Wikland M, Hultén L. Radiological study of changes in the pelvis in women following proctocolectomy. *Int J Colorectal Dis* 1991; **6**: 103-107 [PMID: 1875117 DOI: 10.1007/BF00300204]

21 **Cornish JA**, Tan E, Teare J, Teoh TG, Rai R, Darzi AW, Paraskevas P, Clark SK, Tekkis PP. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007; **50**: 1128-1138 [PMID: 17588223 DOI: 10.1007/s10350-007-0240-7]

22 **Waljee A**, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006; **55**: 1575-1580 [PMID: 16772310 DOI: 10.1136/gut.2005.090316]

23 **Johnson P**, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2004; **47**: 1119-1126 [PMID: 15164254 DOI: 10.1007/s10350-004-0570-7]

24 **Lepistö A**, Sarna S, Tiitinen A, Järvinen HJ. Female fertility and childbirth after ileal pouch-anal anastomosis for ulcerative colitis. *Br J Surg* 2007; **94**: 478-482 [PMID: 17310506 DOI: 10.1002/bjs.5509]

25 **Ahmad G**, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, Wiseman D. Barrier agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2008; : CD000475 [PMID: 18425865]

26 **Fréour T**, Miossec C, Bach-Ngohou K, Dejoie T, Flamant M, Maillard O, Denis MG, Barriere P, Bruley des Varannes S, Bourreille A, Masson D. Ovarian reserve in young women of reproductive age with Crohn's disease. *Inflamm Bowel Dis* 2012; **18**: 1515-1522 [PMID: 21936034 DOI: 10.1002/ibd.21872]

27 **Şenateş E**, Çolak Y, Erdem ED, Yeşil A, Coşkunpınar E, Şahin Ö, Altunöz ME, Tuncer I, Kurdaş Övünç AO. Serum anti-Müllerian hormone levels are lower in reproductive-age women with Crohn's disease compared to healthy control women. *J Crohns Colitis* 2013; **7**: e29-e34 [PMID: 22472089 DOI: 10.1016/j.crohns.2012.03.003]

28 **Sills ES**, Tucker MJ. First experience with intracytoplasmic sperm injection for extreme oligozoospermia associated with Crohn's disease and 6-mercaptopurine chemotherapy. *Asian J Androl* 2003; **5**: 76-78 [PMID: 12647009]

29 **Agret F**, Cosnes J, Hassani Z, Gornet JM, Gendre JP, Lémann M, Beaugerie L. Impact of pregnancy on the clinical activity of Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 509-513 [PMID: 15740532 DOI: 10.1111/j.1365-2036.2005.02384.x]

30 **Thomas GA**, Rhodes J, Green JT, Richardson C. Role of smoking in inflammatory bowel disease: implications for therapy. *Postgrad Med J* 2000; **76**: 273-279 [PMID: 10775279 DOI: 10.1136/pmj.76.895.273]

31 **Bortoli A**, Pedersen N, Duricova D, D'Inca R, Gionchetti P, Panelli MR, Ardizzone S, Sanroman AL, Gisbert JP, Arena I, Riegler G, Marrollo M, Valpiani D, Corbellini A, Segato S, Castiglione F, Munkholm P. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Aliment Pharmacol Ther* 2011; **34**: 724-734 [PMID: 21815900 DOI: 10.1111/j.1365-2036.2011.04794.x]

32 **Moser MA**, Okun NB, Mayes DC, Bailey RJ. Crohn's disease, pregnancy, and birth weight. *Am J Gastroenterol* 2000; **95**: 1021-1026 [PMID: 10763954 DOI: 10.1111/j.1572-0241.2000.01852.x]

33 **Morales M**, Berney T, Jenny A, Morel P, Extermann P. Crohn's disease as a risk factor for the outcome of pregnancy. *Hepatogastroenterology* 2000; **47**: 1595-1598 [PMID: 11149010]

34 **Julsgaard M**, Nørgaard M, Hvas CL, Buck D, Christensen LA. Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis. *Inflamm Bowel Dis* 2011; **17**: 1573-1580 [PMID: 21674714 DOI: 10.1002/ibd.21522]

35 **Riis L**, Vind I, Politi P, Wolters F, Vermeire S, Tsianos E, Freitas J, Mouzas I, Ruiz Ochoa V, O'Morain C, Odes S, Binder V, Moum B, Stockbrügger R, Langholz E, Munkholm P. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 1539-1545 [PMID: 16863558 DOI: 10.1111/j.1572-0241.2006.00602.x]

36 **Castiglione F**, Pignata S, Morace F, Sarubbi A, Baratta MA, D'Agostino L, D'Arienzo A, Mazzacca G. Effect of pregnancy on the clinical course of a cohort of women with inflammatory bowel disease. *Ital J Gastroenterol* 1996; **28**: 199-204 [PMID: 8842834]

37 **Nwokolo CU**, Tan WC, Andrews HA, Allan RN. Surgical resections in parous patients with distal ileal and colonic Crohn's disease. *Gut* 1994; **35**: 220-223 [PMID: 8307473 DOI: 10.1136/gut.35.2.220]

38 **Munkholm P**. Pregnancy, fertility, and disease course in patients with Crohn's disease and ulcerative colitis. *Eur J Intern Med* 2000; **11**: 215-221 [PMID: 10967510 DOI: 10.1016/S0953-6205(00)00088-1]

39 **Kane S**, Kisiel J, Shih L, Hanauer S. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. *Am J Gastroenterol* 2004; **99**: 1523-1526 [PMID: 15307871 DOI: 10.1111/j.1572-0241.2004.30472.x]

40 **Kane S**, Lemieux N. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2005; **100**: 102-105 [PMID: 15654788 DOI: 10.1111/j.1572-0241.2005.40785.x]

41 **Moffatt DC**, Ilnyckyj A, Bernstein CN. A population-based study of breastfeeding in inflammatory bowel disease: initiation, duration, and effect on disease in the postpartum period. *Am J Gastroenterol* 2009; **104**: 2517-2523 [PMID: 19550409 DOI: 10.1038/ajg.2009.362]

42 **Nørgård B**, Pedersen L, Christensen LA, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007; **102**: 1406-1413 [PMID: 17437503 DOI: 10.1111/j.1572-0241.2007.01216.x]

43 **Cornish J**, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830-837 [PMID: 17185356 DOI: 10.1136/gut.2006.108324]

44 **Dominitz JA**, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. *Am J Gastroenterol* 2002; **97**: 641-648 [PMID: 11926208 DOI: 10.1111/j.1572-0241.2002.05543.x]

45 **Ilnyckyji A**, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. *Am J Gastroenterol* 1999; **94**: 3274-3278 [PMID: 10566729 DOI: 10.1111/j.1572-0241.1999.01537.x]

46 **Nguyen GC**, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009; **7**: 329-334 [PMID: 19027089 DOI: 10.1016/j.cgh.2008.10.022]

47 **Chambers CD**, Tutuncu ZN, Johnson D, Jones KL. Human pregnancy safety for agents used to treat rheumatoid arthritis: adequacy of available information and strategies for developing post-marketing data. *Arthritis Res Ther* 2006; **8**: 215 [PMID: 16774693 DOI: 10.1186/ar1977]

48 **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]

49 **Moskovitz DN**, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. *Am J Gastroenterol* 2004; **99**: 656-661 [PMID: 15089898 DOI: 10.1111/j.1572-0241.2004.04140.x]

50 **Nørgård B**, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007; **102**: 1947-1954 [PMID: 17573787]

51 **Hernández-Díaz S**, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 2000; **343**: 1608-1614 [PMID: 11096168 DOI: 10.1056/NEJM200011303432204]

52 **Hernández-Díaz S**, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009; **117**: 185-189 [PMID: 19270786]

53 **Østensen M**, Motta M. Therapy insight: the use of antirheumatic drugs during nursing. *Nat Clin Pract Rheumatol* 2007; **3**: 400-406 [PMID: 17599074 DOI: 10.1038/ncprheum0532]

54 Transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776-789 [PMID: 11533352]

55 **Branski D**, Kerem E, Gross-Kieselstein E, Hurvitz H, Litt R, Abrahamov A. Bloody diarrhea--a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* ; **5**: 316-317 [PMID: 2870147 DOI: 10.1097/00005176-198605020-00028]

56 **Mahadevan U**, Kane S. American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006; **131**: 283-311 [PMID: 16831611 DOI: 10.1053/j.gastro.2006.04.049]

57 **van der Woude CJ**, Kolacek S, Dotan I, Oresland T, Vermeire S, Munkholm P, Mahadevan U, Mackillop L, Dignass A. European evidenced-based consensus on reproduction in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 493-510 [PMID: 21122553 DOI: 10.1016/j.crohns.2010.07.004]

58 **Gisbert JP**. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. *Inflamm Bowel Dis* 2010; **16**: 881-895 [PMID: 19885906 DOI: 10.1002/ibd.21154]

59 **Osadchy A**, Koren G. Cyclosporine and lactation: when the mother is willing to breastfeed. *Ther Drug Monit* 2011; **33**: 147-148 [PMID: 21240055]

60 **Mahadevan U**, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011; **106**: 214-23; quiz 224 [PMID: 21157441 DOI: 10.1038/ajg.2010.464]

61 **Torchinsky A**, Shepshelovich J, Orenstein H, Zaslavsky Z, Savion S, Carp H, Fain A, Toder V. TNF-alpha protects embryos exposed to developmental toxicants. *Am J Reprod Immunol* 2003; **49**: 159-168 [PMID: 12797522 DOI: 10.1034/j.1600-0897.2003.01174.x]

62 **Simister NE**. Placental transport of immunoglobulin G. *Vaccine* 2003; **21**: 3365-3369 [PMID: 12850341 DOI: 10.1016/S0264-410X(03)00334-7]

63 **Kane SV**, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol* 2009; **104**: 228-233 [PMID: 19098873 DOI: 10.1038/ajg.2008.71]

64 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]

65 **Arsenescu R**, Arsenescu V, de Villiers WJ. TNF-α and the development of the neonatal immune system: implications for inhibitor use in pregnancy. *Am J Gastroenterol* 2011; **106**: 559-562 [PMID: 21468063 DOI: 10.1038/ajg.2011.5]

66 **Østensen M**, Förger F. Management of RA medications in pregnant patients. *Nat Rev Rheumatol* 2009; **5**: 382-390 [PMID: 19506586 DOI: 10.1038/nrrheum.2009.103]

67 **Cowchock FS**, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. *Am J Obstet Gynecol* 1992; **166**: 1318-1323 [PMID: 1595785 DOI: 10.1016/0002-9378(92)91596-3]

68 **Ogueh O**, Johnson MR. The metabolic effect of antenatal corticosteroid therapy. *Hum Reprod Update* 2000; **6**: 169-176 [PMID: 10782575 DOI: 10.1093/humupd/6.2.169]

69 **Breur JM**, Visser GH, Kruize AA, Stoutenbeek P, Meijboom EJ. Treatment of fetal heart block with maternal steroid therapy: case report and review of the literature. *Ultrasound Obstet Gynecol* 2004; **24**: 467-472 [PMID: 15343606 DOI: 10.1002/uog.1713]

70 **Bar Oz B**, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation* 2001; **71**: 1051-1055 [PMID: 11374400 DOI: 10.1097/00007890-200104270-00006]

71 **Reddy D**, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol* 2008; **103**: 1203-1209 [PMID: 18422816 DOI: 10.1111/j.1572-0241.2007.01756.x]

72 **Branche J**, Cortot A, Bourreille A, Coffin B, de Vos M, de Saussure P, Seksik P, Marteau P, Lemann M, Colombel JF. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis* 2009; **15**: 1044-1048 [PMID: 19137604 DOI: 10.1002/ibd.20858]

73 **Langagergaard V**, Pedersen L, Gislum M, Nørgard B, Sørensen HT. Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: A Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; **25**: 73-81 [PMID: 17229222 DOI: 10.1111/j.1365-2036.2006.03162.x]

74 **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]

75 **Ostensen M**, Hartmann H, Salvesen K. Low dose weekly methotrexate in early pregnancy. A case series and review of the literature. *J Rheumatol* 2000; **27**: 1872-1875 [PMID: 10955326]

76 **Kalb RE**, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; **60**: 824-837 [PMID: 19389524 DOI: 10.1016/j.jaad.2008.11.906]

77 **Srinivasan R**, Akobeng AK. Thalidomide and thalidomide analogues for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009; : CD007350 [PMID: 19370684]

78 **Akobeng AK**, Stokkers PC. Thalidomide and thalidomide analogues for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009; : CD007351 [PMID: 19370685]

79 **Ravid A**, Richard CS, Spencer LM, O'Connor BI, Kennedy ED, MacRae HM, Cohen Z, McLeod RS. Pregnancy, delivery, and pouch function after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2002; **45**: 1283-1288 [PMID: 12394423 DOI: 10.1007/s10350-004-6411-x]

80 **Van Assche G**, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63-101 [PMID: 21122490 DOI: 10.1016/j.crohns.2009.09.009]

81 **Selinger CP**, Eaden J, Selby W, Jones DB, Katelaris P, Chapman G, McDondald C, McLaughlin J, Leong RW, Lal S. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. *J Crohns Colitis* 2013; **7**: e206-e213 [PMID: 23040449 DOI: 10.1016/j.crohns.2012.09.010]

82 **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]

83 **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]

84 **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]

85 **Sato A**, Naganuma M, Asakura K, Nishiwaki Y, Yajima T, Hisamatsu T, Iwao Y, Takebayashi T, Watanabe M, Hibi T. Conception outcomes and opinions about pregnancy for men with inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 183-188 [PMID: 21122503 DOI: 10.1016/j.crohns.2009.10.004]

86 **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]

87 **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]

88 **Farthing MJ**, Dawson AM. Impaired semen quality in Crohn's disease--drugs, ill health, or undernutrition? *Scand J Gastroenterol* 1983; **18**: 57-60 [PMID: 6144170 DOI: 10.3109/00365528309181559]

89 **Karbach U**, Ewe K, Schramm P. [(Quality of semen in patients with Crohn's disease) ]. *Z Gastroenterol* 1982; **20**: 314-320 [PMID: 6126966]

90 **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 DOI: 10.1046/j.0303-4569.2003.00588.x]

91 **Prideaux L**, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2012; **18**: 1340-1355 [PMID: 22069240 DOI: 10.1002/ibd.21903]

92 **Dimitrova D**, Kalaydjiev S, Mendizova A, Piryova E, Nakov L. Circulating antibodies to human spermatozoa in patients with ulcerative colitis. *Fertil Steril* 2005; **84**: 1533-1535 [PMID: 16275264 DOI: 10.1016/j.fertnstert.2005.05.041]

93 **Rossato M**, Foresta C. Antisperm antibodies in inflammatory bowel disease. *Arch Intern Med* 2004; **164**: 2283 [PMID: 15534172 DOI: 10.1001/archinte.164.20.2283]

94 **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 DOI: 10.1097/00000658-200006000-00017]

95 **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 DOI: 10.1159/000085356]

96 **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 DOI: 10.1111/j.1463-1318.2005.00895.x]

97 **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 DOI: 10.1007/s00384-003-0543-7]

98 **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 DOI: 10.1007/s10350-004-6287-9]

99 **Beeley L**. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3**: 23-42 [PMID: 6148848]

100 **Filipović BR**, Filipović BF, Kerkez M, Milinić N, Randelović T. Depression and anxiety levels in therapy-naive patients with inflammatory bowel disease and cancer of the colon. *World J Gastroenterol* 2007; **13**: 438-443 [PMID: 17230615]

101 **Anderson BT**, Ertle JT, Borum ML. Men with inflammatory bowel disease are rarely counseled regarding effects of immunosuppressive therapy on fertility and pregnancy. *J Crohns Colitis* 2013; **7**: e716 [PMID: 24055456 DOI: 10.1016/j.crohns.2013.08.015]

102 **Levi AJ**, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. *Lancet* 1979; **2**: 276-278 [PMID: 88609 DOI: 10.1016/S0140-6736(79)90292-7]

103 **Birnie GG**, McLeod TI, Watkinson G. Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22**: 452-455 [PMID: 6114898 DOI: 10.1136/gut.22.6.452]

104 **Chermesh I**, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36**: 551-552 [PMID: 15334777 DOI: 10.1016/j.dld.2003.11.030]

105 **Taffet SL**, Das KM. Sulfasalazine. Adverse effects and desensitization. *Dig Dis Sci* 1983; **28**: 833-842 [PMID: 6136396 DOI: 10.1007/BF01296907]

106 **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 DOI: 10.1136/gut.25.10.1078]

107 **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 DOI: 10.1007/s003840050093]

108 **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]

109 **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]

110 **Toth A**. Reversible toxic effect of salicylazosulfapyridine on semen quality. *Fertil Steril* 1979; **31**: 538-540 [PMID: 36307]

111 **Toovey S**, Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanism. *Gut* 1981; **22**: 445-451 [PMID: 6114897 DOI: 10.1136/gut.22.6.445]

112 **Kjaergaard N**, Christensen LA, Lauritsen JG, Rasmussen SN, Hansen SH. Effects of mesalazine substitution on salicylazosulfapyridine-induced seminal abnormalities in men with ulcerative colitis. *Scand J Gastroenterol* 1989; **24**: 891-896 [PMID: 2572047 DOI: 10.3109/00365528909089231]

113 **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/gut.28.8.1008]

114 **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]

115 **Di Paolo MC**, Paoluzi OA, Pica R, Iacopini F, Crispino P, Rivera M, Spera G, Paoluzi P. Sulphasalazine and 5-aminosalicylic acid in long-term treatment of ulcerative colitis: report on tolerance and side-effects. *Dig Liver Dis* 2001; **33**: 563-569 [PMID: 11816545 DOI: 10.1016/S1590-8658(01)80108-0]

116 **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]

117 **Ireland A**, Jewell DP. Sulfasalazine-induced impotence: a beneficial resolution with olsalazine? *J Clin Gastroenterol* 1989; **11**: 711 [PMID: 2573629]

118 **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 DOI: 10.1053/gast.2001.28692]

119 **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]

120 **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 DOI: 10.1111/j.1572-0241.2000.01846.x]

121 **Kane SV**. What's good for the goose should be good for the gander--6-MP use in fathers with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 581-582 [PMID: 10710042]

122 **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]

123 **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]

124 **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]

125 **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]

126 **Türk G**, Ateşşahin A, Sönmez M, Yüce A, Ceribaşi AO. Lycopene protects against cyclosporine A-induced testicular toxicity in rats. *Theriogenology* 2007; **67**: 778-785 [PMID: 17123593 DOI: 10.1016/j.theriogenology.2006.10.013]

127 **Türk G**, Sönmez M, Ceribaşi AO, Yüce A, Ateşşahin A. Attenuation of cyclosporine A-induced testicular and spermatozoal damages associated with oxidative stress by ellagic acid. *Int Immunopharmacol* 2010; **10**: 177-182 [PMID: 19883798 DOI: 10.1016/j.intimp.2009.10.013]

128 **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]

129 **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]

130 **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]

131 **Thomas E**, Koumouvi K, Blotman F. Impotence in a patient with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 2000; **27**: 1821-1822 [PMID: 10914881]

132 **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]

133 **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]

134 **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 DOI: 10.1080/01485010490250533]

135 **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]

136 **Grunewald S**, Paasch U, Glander HJ. Systemic dermatological treatment with relevance for male fertility. *J Dtsch Dermatol Ges* 2007; **5**: 15-21 [PMID: 17229200 DOI: 10.1111/j.1610-0387.2007.06169.x]

137 **French AE**, Koren G. Effect of methotrexate on male fertility. *Can Fam Physician* 2003; **49**: 577-578 [PMID: 12790266]

138 **Sussman A**, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215-217 [PMID: 7356357 DOI: 10.1001/archderm.1980.01640260091025]

139 **Günther E**. [Andrologic examinations in the antimetabolite therapy of psoriasis]. *Dermatol Monatsschr* 1970; **156**: 498-502 [PMID: 5509154]

140 **Grunnet E**, Nyfors A, Hansen KB. Studies of human semen in topical corticosteroid-treated and in methotrexate-treated psoriatics. *Dermatologica* 1977; **154**: 78-84 [PMID: 852624 DOI: 10.1159/000251036]

141 **De Luca M**, Ciampo E, Rossi A. [Study of the seminal fluid in subjects treated with methotrexate]. *G Ital Dermatol Minerva Dermatol* 1971; **46**: 247-249 [PMID: 5109609]

142 **El-Beheiry A**, El-Mansy E, Kamel N, Salama N. Methotrexate and fertility in men. *Arch Androl* 1979; **3**: 177-179 [PMID: 518200 DOI: 10.3109/01485017908985067]

143 **Schrader M**, Müller M, Straub B, Miller K. The impact of chemotherapy on male fertility: a survey of the biologic basis and clinical aspects. *Reprod Toxicol* 2001; **15**: 611-617 [PMID: 11738514 DOI: 10.1016/S0890-6238(01)00182-4]

144 . Rubin PC. Prescribing in pregnancy. London: BMJ Books, 2000.

145 **Mahadevan U**. Fertility and pregnancy in the patient with inflammatory bowel disease. *Gut* 2006; **55**: 1198-1206 [PMID: 16849349 DOI: 10.1136/gut.2005.078097]

146 **Janssen NM**, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* 2000; **160**: 610-619 [PMID: 10724046 DOI: 10.1001/archinte.160.5.610]

147 . Koo JYM, Lee CS, Lebwohl M. Mild-to-moderate psoriasis, 2nd ed. New York: Informa Healthcare, 2009.

148 **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 DOI: 10.1136/pgmj.62.726.269]

149 **Mogilner JG**, Elenberg Y, Lurie M, Shiloni E, Coran AG, Sukhotnik I. Effect of dexamethasone on germ cell apoptosis in the contralateral testis after testicular ischemia-reperfusion injury in the rat. *Fertil Steril* 2006; **85** Suppl 1: 1111-1117 [PMID: 16616082 DOI: 10.1016/j.fertnstert.2005.10.021]

150 **Said TM**, Agarwal A, Falcone T, Sharma RK, Bedaiwy MA, Li L. Infliximab may reverse the toxic effects induced by tumor necrosis factor alpha in human spermatozoa: an in vitro model. *Fertil Steril* 2005; **83**: 1665-1673 [PMID: 15950634 DOI: 10.1016/j.fertnstert.2004.11.068]

151 **Perdichizzi A**, Nicoletti F, La Vignera S, Barone N, D'Agata R, Vicari E, Calogero AE. Effects of tumour necrosis factor-alpha on human sperm motility and apoptosis. *J Clin Immunol* 2007; **27**: 152-162 [PMID: 17308869 DOI: 10.1007/s10875-007-9071-5]

152 **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]

153 **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]

154 **Lampiao F**, du Plessis SS. TNF-alpha and IL-6 affect human sperm function by elevating nitric oxide production. *Reprod Biomed Online* 2008; **17**: 628-631 [PMID: 18983746]

155 **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]

156 **Miehsler W**, Novacek G, Wenzl H, Vogelsang H, Knoflach P, Kaser A, Dejaco C, Petritsch W, Kapitan M, Maier H, Graninger W, Tilg H, Reinisch W. A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 221-256 [PMID: 21122513 DOI: 10.1016/j.crohns.2009.12.001]

157 **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 DOI: 10.1191/096032700678815765]

158 **Wildi LM**, Haraoui B. Reversible male infertility under treatment with an anti-TNFα agent: a case report. *Ann Rheum Dis* 2012; **71**: 473-474 [PMID: 22138196 DOI: 10.1136/annrheumdis-2011-200299]

**P-Reviewers:** Hakonarson H, ZhangLH **S-Editor:** Wen LL  **L-Editor:**  **E-Editor:**

**Table 1 Drugs in pregnancy and breastfeeding**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **FDA** | **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 |
| Azathioprine/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 months prior to conception. |
| Corticosteroids | C | Safe | Safe | Very low risk of malformations. If possible, not use for long. |
| 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 |  |

ECCO: European Crohn's Colitis Organisation.

**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 reversibile case | No reports | No recommendations to discontinue prior to conception. |
| Sulfasalazine | Single case | Yes, reversibile, not dose dependent | One study | Switch to other 5-ASA preparations. |
| Azathioprine/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 months prior to conception. |
| Steroids | No reports | No | No reports | Lack of data to discontinue. |
| TNF-α 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. |